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TUBERCULOSIS IN THE HUMAN LUNG, LIVER,
SPLEEN, ETC.

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✓
By H. D. SCHMIDT, M.D.

Pathologist to the Charity Hospital, New Orleans.



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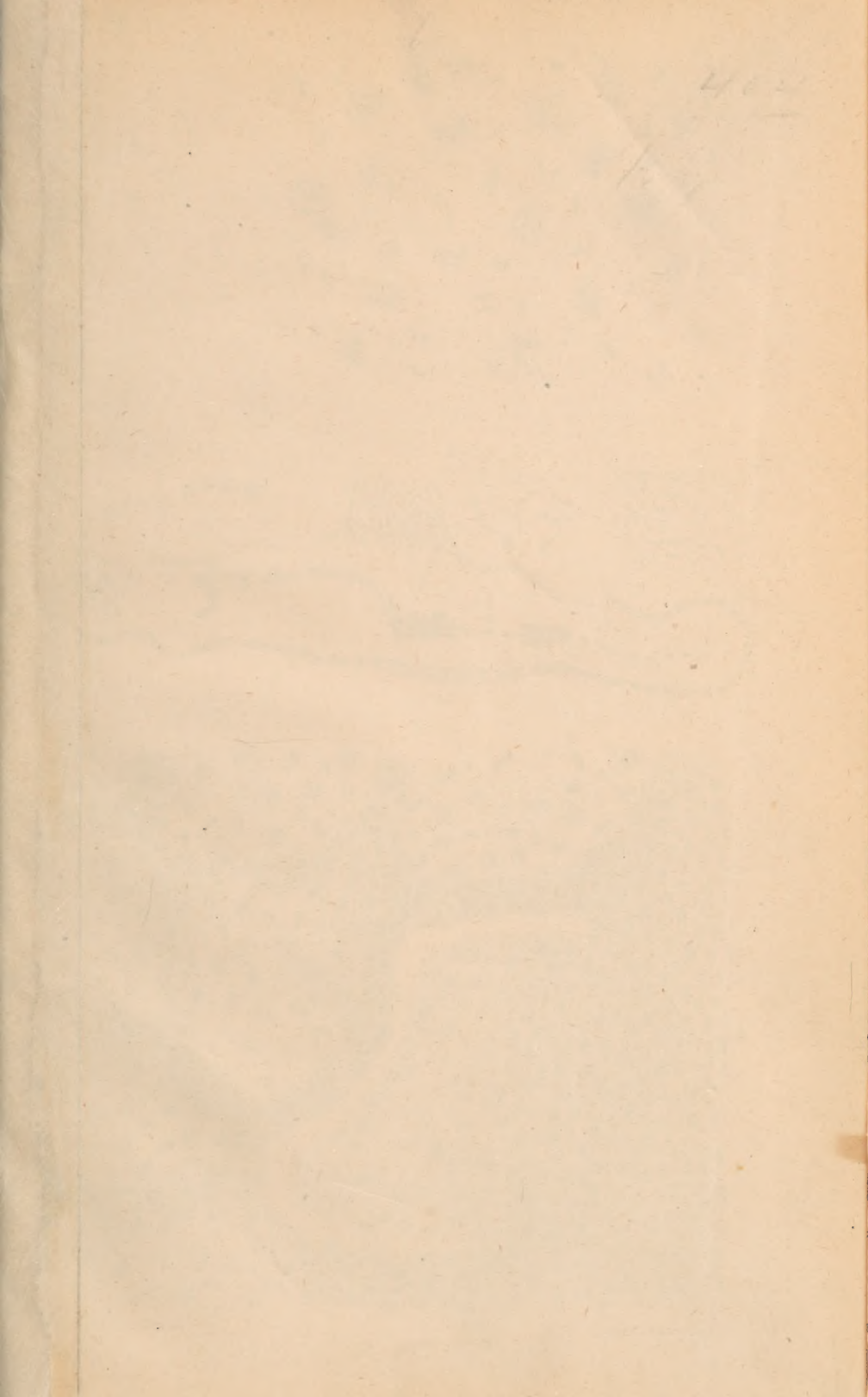
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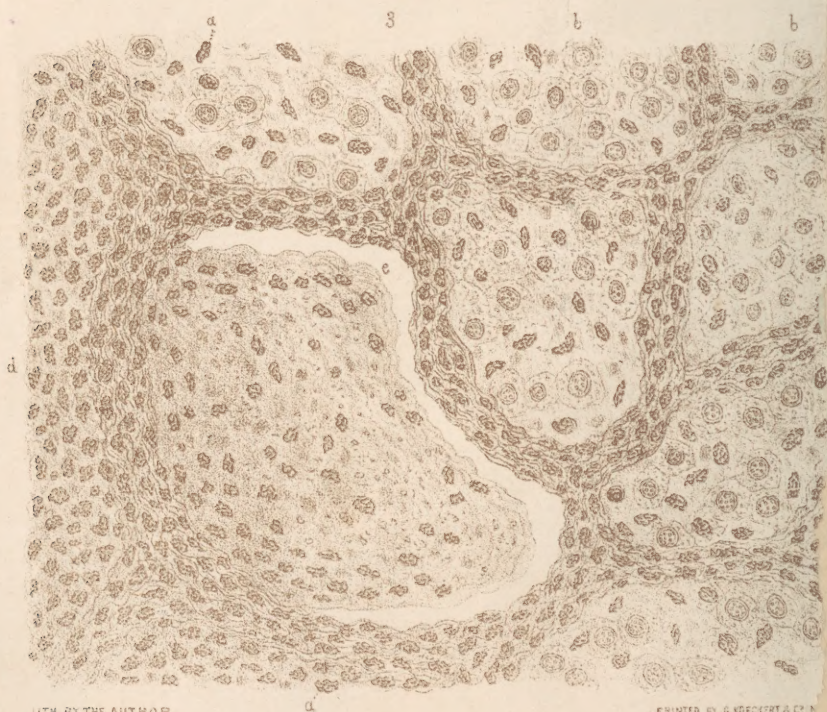
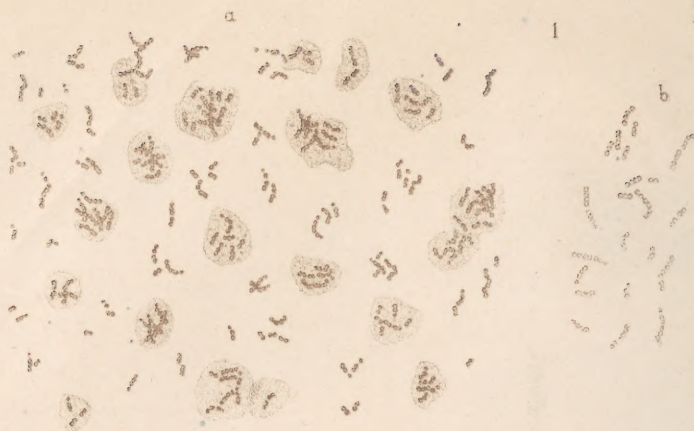
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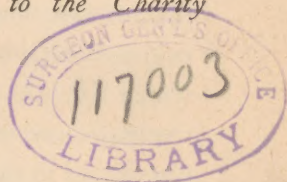


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ORIGIN AND DEVELOPMENT —OF THE— BACILLUS TUBERCULOSIS

In the Human Lung, Liver, Spleen, Etc.

By H. D. SCHMIDT, M.D., *Pathologist to the Charity
Hospital, New Orleans.*



INTRODUCTION.

In the following pages I shall state the results of a series of microscopical researches, which, since April, 1883, I have made in regard to the nature of the so-called bacillus tuberculosis of Koch, and to the true relationship of this

* The investigations described in this treatise were commenced in the spring of 1883, and continued to the beginning of July, 1884, by which time the author had closely studied the lungs and other organs of twelve or more cases of both miliary and chronic tuberculosis, besides having elicited the principal facts concerning the relation of the bacillus tuberculosis to the tissues of these organs. At this time, however, his expectations of seeing the results of these labors in print during the following winter were dwarfed by a fresh and severe attack of his old enemy, the rheumatism, which kept him confined to his couch for four long and weary months. When, in the ensuing autumn, he was again enabled to resume his accustomed labors, he resolved to render his observations more valuable by the special study of the organs of about fifteen more cases of tuberculosis, and by devoting more time to the preparation of the treatise and the execution of the accompanying illustrations than he had at first intended.

organism to the tissues of the human tuberculous lung, liver, spleen, etc. These researches may be regarded as a continuation of some others which I made during the summer and autumn of 1882, and the results of which were published in two articles in December, 1882, and February, 1883, in the CHICAGO MEDICAL JOURNAL AND EXAMINER.

Before, however, commencing to speak of these more recent researches on this subject, I deem it proper to present to the reader a few explanatory remarks on the statements concerning the bacillus tuberculosis of Koch, which I made in the two papers just mentioned.

It will be remembered by those who read these papers that, at that time, I failed to demonstrate the bacillus tuberculosis in sections of tuberculous lung, stained by the method which Koch had recommended in his paper, but that by treating these sections with a solution of caustic potash I discovered in the tubercles certain characteristic cells which contained, besides fat-globules and pigment-granules, numerous minute fat crystals. These crystals, representing very minute rods, so closely resembled in form minute bacilli that, as Koch had not mentioned them in his paper, they induced me to regard them as identical with the organisms which Koch had described. This error, as I have already remarked in my second paper, and as I may now repeat, would never have been committed if I had had the opportunity, before taking the above view, of actually seeing Koch's bacillus tuberculosis, or, if Koch, in naming the organism which he had discovered in human tuberculous lungs as well as in the expectorations of tuberculous patients, had considered a little closer the characteristic features of a bacillus, such as they have been defined by Cohn

in his classification of the bacteria family. I would not venture to express myself so fully on this subject if I had succeeded to see in only one instance among the thousands of these so-called bacilli tuberculosis, which I have now stained and examined in sections of tuberculous lung and in specimens of tuberculous expectoration, the features displayed which characterize the bacillus form of a bacterium. On the contrary, in every instance I found, not only the form, but all other characteristic features of a so-called spherobacterium. Instead of these organisms appearing in the form of minute rods, such as Koch has described them, they represent in reality shorter or longer filaments composed of minute granules. This granular composition of the bacillus tuberculosis of Koch was first observed by Gibbs, and published in August, 1882, in the *London Lancet*. But I must confess that my faith in the true bacillus form of the organism in question, as described by Koch himself, was at that time so great as to incline me to think that the granular filaments, mentioned by Gibbs, did not truly represent the rod-like bacillus tuberculosis of Koch. And accordingly, when I came to observe these granular filaments in tuberculous sputa, treated with a solution of caustic potash, I regarded them as the organisms mentioned by Gibbs, without ever suspecting them to be representations of the veritable bacillus tuberculosis of Koch. Guided then in microscopical examinations by the idea that the bacillus tuberculosis of Koch must show itself in the form of a minute rod, such as its name implies, it must not be wondered that, when discovering in certain degenerating cells of the tubercles minute rod-like fat crystals, which in form closely resembled minute bacilli, the idea arose in my mind

that they might be identical with Koch's bacillus tuberculosis. This idea was strengthened not only by the fact that the cells containing these crystalline pseudo-bacilli were met with in the very places where Koch had located his bacillus tuberculosis, that is, along the periphery of the tubercle and outside of the cheesy centre, but moreover by these peculiar cells never having been mentioned in his paper. In the course of this treatise I shall have opportunity to refer again to these cells, which, as far as I know at present, are not identical with the true neoplastic cells of the tubercle, but which, nevertheless, are not without significance in the histological development of this neoplasm. When finally, in January, 1883, the true bacillus tuberculosis of Koch was shown to me in a specimen of tuberculous pus-tum, such as I mentioned in my second paper on the subject, I found that it was identical with the granular filaments to which Gibbs had referred in his paper, I did not hesitate to acknowledge this fact.

More than three years have passed since my second paper on this subject was published, in which I notified the reader that I should take up the subject again as soon as I should have procured the proper staining material, and not rest until I should have either satisfied myself as to the existence of this pretended parasite, or at least have thrown some light upon the different forms under which it had appeared to different observers. Since that time the bacillus tuberculosis has been a common object of microscopical examination, and thousands of specimens of tuberculous sputum have been stained and examined, and numerous articles written and lectures delivered on the results of these microscopical examinations. But as they were, with a comparatively

few exceptions, chiefly made by clinicians for diagnostic purposes, with the view of simply determining the presence or absence of the bacillus tuberculosis in the lungs of their patients, no further light was thrown upon the true origin of the organism, or upon the manner in which it gained access into the human lungs. Nor have the hundreds of thousands of inoculations with tuberculous matter, hitherto made on various kinds of animals, demonstrated anything more than the empirical fact of the presence or absence of the bacillus tuberculosis in the lungs or other organs of the inoculated animal, proving simply the transferability of tuberculosis from one animal to the other. The study of this minute, apparently parasitic organism in the human lungs, the most important locality where it is met with, appears to have been greatly neglected. Those investigators, even, who studied this organism in the tissues of these organs, appeared to have cared mainly to satisfy themselves as to its presence or absence in the latter, for, if their histological labors had been carried on more closely, they would not have failed to observe certain facts which closely bear on the nature and development, and even origin, of these bacteria, and which in the following pages, will form the chief part of my subject.

From the remarks just made it may then be inferred that while much has been done, since Koch first announced his discovery of the bacillus tuberculosis, by way of clinical observation and experimental pathology, to solve the so-called bacillus tuberculosis question, the microscopical research in the field of pathological anatomy has, to the extent of my knowledge, rather been neglected. The reason for this negligence, however, may be easily found in considering that the material for clinical observations, as well as for experimen-

tal pathology, is more abundant and more easily obtained than that required for extensive and thorough microscopical researches in pathological anatomy. Every medical practitioner meets with cases of tuberculosis in his daily practice, and as the preparing and staining, as well as the microscopical examination of a little tuberculous sputum, does not require extraordinary skill, nor consume much time, he will have sufficient opportunity of making his own clinical observations on the subject,—while, on the other hand, the material required for extensive investigations in pathological anatomy can only be obtained in connection with the pathological departments of large hospitals. Thus it has happened that so many thousands of specimens of tuberculous sputum have hitherto been examined and discussed in medical societies and journals, while more extensive microscopical studies of thin sections of tuberculous lung, or other organs, have thus far only been made by a comparatively very small number of investigators.

My own labors relating to the bacillus tuberculosis were closely confined to the field of pathological anatomy, for the reason that in this field I am in every respect prepared to do justice to the subject,—not only as regards the abundant fresh pathological material constantly at my disposal, but moreover as regards the proper outfit and assistance for the making of accurate and extensive histological researches. As regards the optical instruments which I use, I may say that during these last twenty-six years I have worked exclusively with first class objectives of the best makers, but especially with those made by the late Mr. Tolles, while the microscopical stands which I have used represent the large patterns made by Mr. Joseph Zentmayer, and constructed for the adaptation of any accessory optical appliance that can facilitate and per-

fect microscopical examinations. I may state that I have complied with Koch's demand in pursuing my special studies of the bacillus tuberculosis with the assistance of a $\frac{1}{6}$ inch homogeneous immersion objective, which, in the summer of 1884, Mr. R. Tolles made for me for this special work. This objective, constructed not for the purpose of resolving the fine lines of diatoms, but for histological work, with a view of obtaining penetration and perfect definition, is, from what I know, if I may be allowed to say in honor of its maker, the equal to any other objective hitherto made. Besides this objective I also made use of Abbe's illuminating apparatus, which Mr. Zentmayer had adapted to my microscope. Both this apparatus and the homogeneous immersion objective, though they are not absolutely essential, I have reason to say with Koch greatly facilitate an accurate study of the bacillus tuberculosis and its relations. In my own case they proved of great service in confirming the correctness of the observations which I had previously made with dry or water immersion objectives, and a Powel and Lecland's homogeneous achromatic condenser.

In order to properly understand the question of living germs of disease, it is necessary that the reader should be familiar, to a certain extent, with the exact definition of the different forms of bacteria upon which the classification of these organisms is based. Unfortunately the great majority of practicing physicians are unacquainted with the difference of form, or other characteristic features, existing between these minute organisms, which by many physicians are regarded as the original cause of a now considerable number of diseases: for, as they look upon these beings only from a practical point of view, it matters to them very little whether the living germ appears in the form of a sphero-bacterium, or in that of a

bacillus. To them the monas tuberculosis of Klebs, the micrococcus tuberculosis of Toussaint and the bacillus tuberculosis of Koch are one and the same in point of signification, as all three have been presented to them as the original cause of tuberculosis. And it is not improbable that the practical physician, in confounding these forms with one another, has come nearer to the truth than the speculating and theorizing bacteriologist. Nevertheless, in treating our subject more philosophically and from a pathological point of view, it is very important that we should be precise in the terms we use and see that they closely correspond with the true definition of the object in question. For this reason, I shall, before proceeding to the description of my observations, make a few passing remarks on the morphological characters of the different kinds of bacteria and their transformation from one form into another.

Although several attempts have been made by divers naturalists to arrange the different kinds of bacteria (Schizomycetes, cleft fungi) according to their form, or other prominent characters, into a number of systematic groups, no perfect classification of these organisms has hitherto been attained. The reason of this failure is to be found in the want of permanency in the various forms under which the bacteria, such as they occur in nature, present themselves to the eye of the observer. The classification which has been most generally used, on account of its convenience for practical purposes, and which for this reason I have formally followed myself, is that of Cohn. It is chiefly based upon the morphological character of the organisms concerned, and consists of the following four groups: 1, *Spherobacteria*, appearing in the form of minute spherical, or oval, cells, the diameter of which is generally less than 0.00 mill. They either appear singly or

adhering to one another in pairs, or in chains, formed by a smaller or greater number of cells. When their multiplication by the division of the individual cells becomes very active, they aggregate into masses, or colonies, generally called "zoglœa," which are embedded in a gelatinous material, secreted by the cells. This group embraces but one genus, that of *micrococcus*; 2, *Microbacteria*, embracing, in a narrow sense, the single genus *Bacterium*, represented by short cylindrical, or elliptical cells, which also hang together in pairs. They very rarely appear in the form of chains, though they are met with in the form of zoglœa with abundant intercellular substance; 3, *Desmobacteria*, represented by straight cylindrical cells, usually much longer than wide. They occur isolated, but are usually united in chains. While some of them exhibit active spontaneous movements, others appear motionless. They are represented by the genera *Bacillus* and *Vibrio*; 4, *Spirobacteria*, appearing in the form of cylindrical cells, generally several times as long as wide, and spirally around, similar to a corkscrew. They embrace the genera *Spirillum* and *Spirochæte*. There are a number of other genera of the cleft fungi which, however, may be passed over for the sake of brevity.

When Cohn conceived the above classification of the bacteria, he regarded each of these forms as a distinct separate genus, the individuals of which would under all circumstances not only reproduce the same forms, but be also endowed with the same physiological properties. In accordance with this view, germ theorists attributed a specific property of producing one or the other specific disease to each form of pathogenic bacteria. More recent investigations, however, have shown that this view is erroneous, and that the forms and other characters of these genera are by no means permanently fixed, but that,

on the contrary, one form may, in the course of development, be converted into another. Thus, a bacillus may be developed from a micrococcus, and finally divide again into smaller cells to reassume the micrococcus form. The idea of different forms of bacteria representing but different phases of development of a single natural germ was already advanced, more than ten years ago, by Billroth and some other mycologists; but it was particularly upheld by Nägeli, who pointed out the probability that the various forms, under which the schyzomycetes, or cleft fungi, present themselves, might actually represent but a few natural genera. Nägeli's view that not only the forms of the bacteria, but also their physiological properties, may be altered by artificial cultivation in different nutritive media, was subsequently corroborated by the interesting experiments of Hans Buchner, which experiments, as far as I am able to judge from the perusal of his writings, were made with accuracy, necessary precautions and perseverance. These consisted principally in the conversion of the so-called infectious *bacillus anthracis* into the harmless, non-infectious hay-bacillus, or *bacillus subtilis*. This conversion Buchner effected by supplying the former very freely with oxygen during its cultivation, first in a solution of Liebig's extract of meat, pepton and sugar and afterwards in an infusion of hay. These cultivations were carried through 1,500 generations of the fungus in a space of six months. On the other hand, Buchner converted the non-infectious hay-bacillus, such as it occurs in nature, into the infectious bacillus anthracis by cultivating it, first in egg-albumen and solution of meat extract, and then finishing the cultivation in fresh blood taken from rabbits. He furthermore demonstrated very closely the changes taking place in the form of the bacteria; that is, in the length and width of their individual cells or joints, when cultivated in different nutritive

substances. The results which Buchner obtained from his experiments, concerning the convertibility of infectious into non-infectious bacteria, and *vice versa*, and which so conclusively confirmed Nägeli's views regarding the constancy or inconstancy of the forms and physiological properties of these organisms, were, as ought to have been expected, severely criticised by those mycologists who upheld the theory of the specificity of form and property, among whom were Koch and his followers. But the arguments, directed by Koch himself, against the trustworthiness of Buchner's investigations, and calculated to invalidate the facts brought to light by the labors of this investigator, were answered by Buchner in a lengthy but very able treatise, in which, by reviewing and analyzing, in a clear, scientific style, every single point in the charges made against his method of investigation, he deprived the arguments of his opponents of every trace of foundation.

The investigations of Buchner were followed by a series of others, made by Zopf on the highest developed forms of the cleft fungi, viz., *Cladothrix*, *Crenothrix* and *Beggiatoa*, the results of which fully corroborated the view held by Billroth, Nägeli, Buchner, and others. The investigations of Zopf consisted in carefully cultivating the named genera of schizomyces for the purpose of obtaining each individual germ in a pure condition; that is, isolated from individuals belonging to another genus, or species. The numerous microscopical examinations, made of the fungi concerned during their development, showed him that not only micrococci would grow into bacilli, or the latter be converted into the former, but that even the sword and screw-like forms of the spirilla and spirochæte would appear in one and the same genus during the course of development. The interesting and important results which Zopf obtained from his extensive researches into the development of

the cleft fungi and cleft algæ, were published by him in the form of a treatise, fully illustrated by seven beautifully executed lithographic plates* Subsequently to this treatise he published another on the cleft fungi in particular,† in which he treats in a systematic style of the history, anatomy and classification of these organisms. In this little work the subject is treated from the most recent standpoint, based upon the latest observations on the schizomycetes. I do not hesitate to say that I have gained from this little work more definite and positive information, as regards the morphology and nature of bacteria, than from all other works and treatises on the subject I had previously read. Not only this, but certain phenomena which I had observed on different occasions, and for which I was unable to find a satisfactory explanation in other works, were rendered clear to me by the writings of Zopf. These phenomena I observed with bacteria contained in urine, and, as they relate to the subject, I may here briefly state some of them. Bacteria, as is generally known, are very often met with in pathological urine, into which, it is commonly believed, they gain access from the surrounding air, after this fluid has been voided from the bladder. This is probably true in most instances, though, sometimes, I have suspected the reverse, and, in one particular case, in which these organisms were observed in the urine in very great numbers, I convinced myself of their being present in this fluid before its leaving the bladder, by microscopically examining it directly after it was voided. At any rate, from what I know from the numerous

* Zopf. Zur Morphologie der Spaltpflanzen. (Spaltpilze und Spaltalgen.) Verlag von Veit & Comp. Leipzig, 1882.

† Zopf, "Die Spaltpilze."—Nach dem neuesten Standpunkte bearbeitet. Separatabdruck aus der Encyclopædie der Naturwissenschaften. Verlag von Eduard Trewendt, 1883.

specimens of pathological urine which are daily microscopically examined under my supervision at the pathological laboratory of the Charity Hospital, the number of these organisms varies very greatly in the different specimens of urine, collected at one and the same morning, for, while some may be met with in one specimen, and a small number only in the second, they may appear in very great numbers in the third. This fact, which I have observed for years, shows that the absence, or presence in greater or lesser number of the bacteria in the urine, stand in some relationship to the particular condition or constitution of this fluid. The bacterium generally met with is a small micrococcus (fig. 2 *a*) to which the name *micrococcus urinæ* has been applied, though, as it appears to me, it hardly differs in form from those bacteria generally met with in putrefactive liquids. The filaments of the ordinary urine bacteria are straight, and exhibit spontaneous movements. In many specimens of urine, however, a small number of another form of bacteria is met with, the individual filaments of which are seen scattered among the more numerous regular urine bacteria. These (fig. 2 *b*) are distinguished from the latter by their cells being slightly larger and adhering but very loosely to one another, making them appear like rows of beads; they are, moreover, slightly curved, and exhibit no spontaneous movements, resembling, on the whole, the filaments of *mycoderma aceti*. About two years ago I met these torula-form bacteria in very great numbers in a specimen of albuminous urine, in which the number of the regular urine-bacteria was so small as to be hardly noticed. Desiring to know the ultimate fate of the former I kept this urine for a further study. In re-examining it, accordingly, on the next day, I found these torula-form bacteria considerably increased in number, and, furthermore, that many of them had grown into long filaments (fig.

2 c.); on the third day these were also found to have very considerably increased in number. Subsequent microscopical examination revealed another kind of cells (fig. 2 d, and e.), which appeared to have arisen from the long bacterial filaments, as the bottle containing the urine had remained closed. These last cells appeared to represent true torulæ, multiplying, as the drawing shows, both by budding and by cell-division. A final examination, made some days afterward, showed another formation consisting in a number of long filaments, probably representing gelatinous envelopes, in which a number of small groups of micrococci (fig. 2 f.) were observed embedded. It is not improbable that these groups of micrococci originated by the breaking up of larger cells, such as Zopf observed in his investigations.

The above stated observations, which I made on the transformation of bacteria in urine, are too imperfect in themselves to sustain my particular theory, though they are sufficiently correct to corroborate to a certain extent the observations of Zopf and others. My principal object in mentioning them in this place, however, was not to attempt a corroboration of the facts observed by others, but rather to show that valuable information regarding the nature of bacteria may even be gained by casual observations made on these organisms when met with in those liquids in which they naturally occur. A thorough investigation of the whole subject, of course, cannot be made without having recourse to artificial cultivation,—a laborious task, for which I have never had the necessary time and convenience at my disposal.

From what I have said in the foregoing pages, then, we may safely infer that the metamorphosis of one form of

bacteria into the other, first pointed out a number of years ago by Billroth and Nägeli, has been proved finally by the labors of Cienkowski, Nealsen, Buchner and Zopf to be a fact. The important bearing of this fact on the artificial cultivation of pathogenic bacteria, and with it on the whole question of living disease germs is obvious, as it shows the possibility of changing the form in which these bacteria in reality exist in the human organism, by transferring them to another nutritive substratum. While thus, for instance, the so-called bacillus tuberculosis may exist in the human lungs in the form of a micrococcus, it may be developed into a rod or bacillus form, when artificially cultivated in another nutritive medium.

Having by the foregoing introductory remarks prepared the reader for a better appreciation of the results of my recent investigations concerning the nature of the bacillus tuberculosis, and its relationship to the human lungs and other organs, and for the conclusions which may be drawn therefrom, I shall pass over to the description and discussion of my observations.

II.

REMARKS ON THE STAINING OF BACTERIA.

In connection with the demonstration of the bacillus tuberculosis in the thousands of specimens of tuberculosis expectoration, to which I have already referred, a great deal has been said and written on the comparative merits of the different methods for successfully staining this bacterium, and we are justified in presuming that, at the present time, most physicians are familiar with this subject. For this reason I might confine my remarks concerning the staining of thin sec-

tions of tuberculous tissue, as well as of tuberculous sputum, to a simple statement of the particular method which I employed, if there were not observed in the different anatomical elements of the tissues certain differences in the degree of staining, which demand a more extended discussion of this subject.

It may be safely asserted that in the special study of pathogenic bacteria the process of staining these organisms plays a most essential part, as it is alone by this process that their presence, as well as their comparative number in the tissues of one or the other organ can be safely determined. When the sections of tissues containing bacteria are very thin and treated with solutions of caustic potassa or soda, the organisms may under favorable circumstances be distinguished by a practiced eye from the tissues in which they are buried, though, at the same time, the chances of failure are sufficiently great to render this mode of preparation unreliable for a thorough study of the subject. Besides, in order to determine safely the presence of bacteria in sections of tissue by the aid of these solutions, the organisms should be present in considerable numbers, as, otherwise, they are very apt to escape observation on account of their resemblance to organic granules, or even to very minute fat globules. I, therefore, cannot but fully endorse the importance which Koch has attached to the staining of his bacillus tuberculosis for determining its presence in tuberculous tissues. The demonstration of certain points concerning the origin and development of these bacteria in the human lungs and other organs, which I observed in the course of my recent investigations, likewise depend upon a perfect staining of the tissues under examination.

When Koch first announced the discovery of his bacillus tuberculosis he claimed as one of the specific properties of this organism the capacity for retaining the aniline color by which it has been stained, in preference to any other color to which it may be subsequently exposed. Thus, if the bacillus has been stained in an alkaline solution of methyl blue—the original solution which Koch used—it would afterward refuse to absorb a concentrated watery solution of vesuvin, whilst all other bacteria, with the exception of the bacillus lepræ, would give up the methyl blue and absorb the brown color of the vesuvin.

This specific property, however, the bacillus tuberculosis only possesses to a limited degree, that is, as long as the animal tissues, in which it is lodged, have not absorbed the second stain; for as soon as these tissues are saturated and stained by the solution of vesuvin, the bacillus likewise will, at the expense of the blue, absorb the brown, though perhaps not as readily as the animal tissues. The failures which I experienced, when in 1882 I first attempted to stain the bacillus tuberculosis by Koch's original method, were due to my ignorance of this fact, for leaving, according to Koch's directions, my sections of tuberculosis lung fifteen minutes in the concentrated solution of vesuvin, I might have expected that every bacillus tuberculosis contained in the sections would be colored brown. But my faith in Koch's directions was so great at that time as to regard the keeping of the sections in the solution of vesuvin for not less than fifteen minutes as the proper test for distinguishing the bacillus tuberculosis from other bacteria. When, in the spring of 1883, I had succeeded in perfectly staining this organism by the superior methods of Ehrlich and Gibbes, and by continued practice gained some

experience in the staining of bacteria, I recognized the causes of my former failure. But, being at this time familiar with the appearance of the genuine bacillus tuberculosis of Koch, and remembering that its discovery had been effected by means of the original method of staining of this investigator, I resolved to inquire, at some convenient time, once more into the merits of this method of staining. Accordingly, during the spring of 1884, I put a number of very thin sections of tuberculous lung containing, as I knew from previous stainings with Gibbes' solution of magenta, considerable numbers of bacilli tuberculosis, in Koch's original alkaline solution of methyl blue, and, after having left them there for twenty-four hours, transferred them to a concentrated watery solution of vesuvin. Already, after the lapse of a few minutes, these sections had assumed a dark, dirty, greenish-brown color, which, resisting the action of water or alcohol, had rendered them unfit for examination. As there exist some differences in the aniline preparations, even in those of the same color, and especially in the blue, I came to the conclusion that my methyl blue was not of the same kind as that which Koch had used for his staining, and therefore I made, according to Koch's formula, a fresh solution which I colored with methyl violet. But instead of leaving the sections twenty-four hours in this staining fluid I warmed the latter, such as Koch had also recommended. When perfectly stained the sections were transferred to a concentrated watery solution of vesuvin, in which, however, they were only left three minutes. After their removal from the latter solution they were washed in water, then successively treated with absolute alcohol and oil of cloves, in order to be finally mounted in Canada balsam. The subsequent microscopical examination showed but a very few blue colored bacilli tuberculosis in the sections; the rest had become in-

visible by having absorbed the vesuvin and thus assumed the same color as the tissue in which they were buried. Therefore, then, I stained another set of sections with the same solution, which, however, had been rendered somewhat stronger by the addition of a little more methyl violet. After having been stained in this solution, the sections were washed in water, and individually treated with the solution of vesuvin. In doing so, I first left each section half a minute in the solution of vesuvin after which it was washed in water and then, for about half a minute, put in alcohol for the purpose of removing that portion of the vesuvin which in all Canada balsam mountings is removed from the sections by the action of absolute alcohol and oil of cloves, with which they are previously treated. From the alcohol the sections were then taken, immersed in water and examined by the aid of a strong loupe, in order to ascertain whether some of the blue staining was still remaining. When this was the case the section was replaced in the solution of vesuvin for one-fourth or one-half minute longer, until, with the exception of a few small bluish spots, it was colored brown throughout. The microscopical examinations of these sections, after mounting in Canada balsam, showed that these bluish spots were produced by numerous bacilli tuberculosis, stained blue by the methyl violet. The same results were obtained when, instead of the sections, tuberculous sputum was stained by this method.

The above described experiments with Koch's original bacteria staining fluid conclusively showed me that the bacillus tuberculosis has no claim for the specific property of successfully resisting the displacement of one aniline color, which it had once absorbed, if subsequently exposed to another color. I can not forbear to think, therefore, that I might, perhaps, have been more successful in my first attempts to stain the

bacillus tuberculosis by Koch's original method, in 1882, if I had not so closely followed his own directions; though I do not mean to imply that these directions were entirely wrong, as it is possible that the vesuvin which Koch used for his staining may have differed from that which I obtained, by being less soluble in water.

The original method of Koch for staining bacteria by alkaline liquids has been, to the extent of my knowledge, generally abandoned on account of its being inferior to other methods, particularly to those of Ehrlich and Gibbes. The methyl violet and vesuvin, also, are, for the want of sufficient transparency, inferior to magenta followed by chrysoidin or Bismarck brown, and therefore not suited for accurate research. Nor is the methyl violet sufficiently durable, for when the sections, stained by Koch's method, as above described, were re-examined about two weeks afterwards under the microscope, it was found that the bacilli had completely faded; the methyl violet, by which they had been stained, was observed to be diffused throughout all the surrounding tissue.

The *bacillus tuberculosis*, as is now generally known, may be successfully stained by other methods and staining liquids, described by various authors. A number of these I have used myself, but as they all have been commented on by other writers, I shall confine my further remarks on the subject of staining these bacilli to those particular methods which I have finally preferred for my investigations. Of these I may first mention the original method of Ehrlich, in which the aniline oil plays a prominent part. The *bacillus tuberculosis*, especially when present in tuberculous expectoration, may be successfully stained by Ehrlich's original staining fluid; if there is any disadvantage attending the

staining with this fluid, it is its want of permanency, as the bacilli stained by it are liable to fade soon afterward. It is for this reason that I prefer, especially for staining sections of tuberculous tissue, the staining fluid recommended by Gibbes, which in reality is a modification of Ehrlich's, but which, by the alcohol it contains, is capable of holding a greater quantity of aniline oil in solution, while at the same time it is rendered stronger by containing more of the aniline color. This fluid saturates, so to say, the bacteria with color, and thus postpones their fading to a more distant time; for, as far as I am able to judge by experience, the permanency of the staining is proportionate to the quantity of coloring material absorbed by the bacteria. As regards the particular aniline color to be used for the staining, I prefer the magenta, though I have also had very good results with the hydrochloride of rosaniline, or with the methyl violet. While the rosaniline, however, is too light a color for being readily distinguished under the microscope, especially when the organisms are deeply buried in the tissues, the methyl violet has the disadvantage of being not sufficiently transparent and of being too easily dissolved by the absolute alcohol used for dehydrating the sections before mounting in Canada balsam. Thus it may happen that the organisms, though well stained by the methyl violet at first, may appear but faintly or not at all stained after being mounted in Canada balsam. The magenta, therefore, being sufficiently transparent and, from all I know, one of the most stable of the aniline colors generally used, is more suitable for an accurate study of the bacillus tuberculosis and for a permanent mounting of the sections. For the purpose in view, however, it must be of the best quality. The kind which I use is recog-

nized by its solution presenting a purple color, while another inferior kind presents a more scarlet red. The bacilli tuberculosis stained with the former solution present, also, when examined with daylight, a purple color, while those stained with the latter—that is if stained at all—appear more of a scarlet red.

Though I have generally preferred Gibbes' solution for the staining of my sections, I have not always used it in its original strength. In its full strength, such as is expressed by the original formula, this solution is intended for staining the bacillus tuberculosis in a comparatively very short time, according to Gibbes' directions in one-half hour. With this solution the bacteria, whether contained in tuberculous expectoration or in tuberculous tissues, may be very readily stained, for which reason it is very convenient in many cases. In order, however, to stain the bacillus tuberculosis, especially when contained in tuberculous tissues, in a more thorough and permanent manner, I have found it of greater advantage to leave the sections for a longer time in the staining fluid. But as Gibbes' solution, made after the original formula, contains rather too much of the magenta for this purpose, I have, for the staining of my sections, reduced it in strength by taking only one-half of the quantity of magenta put down in the formula. In this modified staining fluid of Gibbes the sections may be left for twenty hours, or even longer. If the weather is very warm, it may happen that during this time the solution is rendered stronger by the evaporation of the alcohol, and that a surplus of the aniline color is found to adhere to the sections, while these, themselves, appear somewhat shrunk in their extent. In cold weather the staining fluid containing the sections may, on the contrary, be slightly

warmed on a sand-bath, until a delicate vapor is observed to arise from the surface of the fluid, after which the flame is extinguished, and the sections left to cool off with the sand. When the sections are removed from the staining fluid, they are put in distilled water and left there as long as it will remove any surplus aniline color contained in them; they will then appear soft and pliable and not diminished in size. But if, as I have already remarked, too much of the aniline color—in the present case the magenta—is found to adhere to the sections, while they themselves have shrunk in size, no attempt should be made to put them in this condition in the nitric acid solution for the purpose of discoloring them, as this solution is not capable of removing entirely the surplus aniline, nor of rendering the section again soft and pliable, or of making it expand to its original size. The sections, when in this condition, should be placed in alcohol, which easily removes the surplus of the aniline color without injuring the tissues; as soon, however, as this surplus is removed, perhaps in one-half or one minute, they are transferred from the alcohol into distilled water, in which they will be found to expand to their original size, and from which they may now be transferred to the solution of nitric acid.

In treating the sections with the solution of nitric acid—one part of the acid to two parts of water—as first recommended by Ehrlich, some caution has to be observed, for the reason that, if left too long a time in this solution, the nitric acid will in most cases not only remove the stain of the aniline color from the animal tissues, but also from the bacilli tuberculosis. For my own part, I generally leave the sections in the nitric acid solution *only as long* as they are ob-

served to emit a brown precipitate. As soon as the formation of this precipitate ceases, I quickly transfer the sections from the nitric acid solution to the water, in which they may be noticed to part with some of the magenta previously absorbed and which here presents a purple tint. If the sections are now transferred to clean water and made to rest on a white ground, they still appear colored to a certain extent by the magenta, so that one might be tempted to treat them once more with the nitric acid solution, until they are completely discolored. The error committed in pursuing this course, however, becomes evident by taking into consideration that the absolute alcohol, to the action of which the sections must be necessarily exposed in order to be rendered fit for being mounted in Canada balsam, always dissolves and removes a certain part of the aniline color left in the sections by the nitric acid solution. In most cases, therefore, in which the sections have been completely discolored by the nitric acid, very few or no bacilli will be detected in them after being mounted in Canada balsam.

But as it is desirable to know, before mounting the sections in Canada balsam, whether they may be expected to contain stained bacilli tuberculosis, I expose them at once, and before they are stained with the second color, to the action of alcohol. If after this process the sections still show purplish spots, when examined upon a white ground in water, we may be sure of the presence of stained bacilli and, moreover, that they will no more be discolored by the subsequent action of absolute alcohol, to which they must necessarily be exposed before they can be mounted in Canada balsam. The same course is pursued after the sections

have been stained with the second aniline color, be it chrysoidin or Bismarck brown, for, as in the case of magenta, a part of these colors is also lost by the action of the absolute alcohol; while in observing the precaution just mentioned the sections, if not sufficiently stained, may without much inconvenience be replaced in one or the other of these colors, in order to absorb them to the proper degree. For staining the tissues of the sections I prefer Bismarck brown or chrysoidin, for the reason that they are more transparent than vesuvin or methyl blue and therefore better suited for special studies of the bacillus tuberculosis; besides the contrast formed by these colors with the magenta purple of the bacilli is quite sufficient for readily distinguishing these organisms from the tissues containing them. As the length of time for the sections to remain in Bismarck brown or any other color depends, of course, on the strength of the solution it, is difficult to fix exact rules on this point. Each student engaged in the study of tuberculous sections, therefore, should himself determine the time with the aid of his watch, by removing and replacing at certain intervals of time the sections from the staining fluid in order to wash and examine them in water, until they are sufficiently stained; if they remain too long in this fluid the bacilli will, in most instances, also be colored brown.

In the foregoing description of the method which I have generally pursued in staining the bacillus tuberculosis in sections of tuberculous tissues, I have only mentioned the nitric acid solution for decolorizing the animal tissues of these sections. Although this solution answers very well the purpose in view, there is, nevertheless, a considerable disadvantage associated with its action, consisting in the

contraction or shrinking of the sections, which renders them less fit for histological studies. In order to avoid this shrinking of the tissues I have had, in many instances, recourse to one of the other agents known to dissolve the aniline color, contained in the fluid, quite as well as the nitric acid. Of these agents I have particularly made use of the formic acid, first recommended, if I remember rightly, by Watson Cheyne. This acid removes the magenta only from the animal tissues, without in the least degree affecting the stained bacilli; the sections, therefore, can be left in it for several minutes without fear of discoloring them too much; the principal advantage in using this acid, however, is that it does not cause the animal tissues to shrink.

With the modification of Gibbes' solution and in the manner described above I have now not only successfully stained many hundreds of sections of the tuberculous tissue and of specimens of tuberculous expectoration, but also various kinds of liquids and infusions containing other bacteria, as, for instance, those met with in urine. The bacteria contained in these liquids were stained as thoroughly as the bacilli tuberculosis. They have retained their color remarkably well, as in some of my preparations, which were stained two years ago, they can still be distinctly seen. The bacilli tuberculosis contained in sections of tuberculous tissue, if thoroughly stained with the magenta solution will also retain the color a long time, almost for a year or even longer.

The bacteria contained in urine or other liquids may be very easily stained in the following manner: a drop of the liquid is put upon a cover-glass and then left to evaporate upon a sand-bath; upon this one or more drops are suc-

cessively applied and dried in the same manner, until the organic matters contained in the liquid are sufficiently thick for the purpose of staining. But as the stratum thus formed by these matters does not protect the bacteria enclosed within from the action of the nitric acid solution to such an extent as the animal tissues of a section of some tuberculous organ protect the bacilli tuberculosis therein, the cover-glass holding the stratum should be exposed to the action of the nitric acid solution but for a very short time, as otherwise the latter will destroy the aniline color previously absorbed by the bacteria.

Before closing my remarks on the process of staining the bacillus tuberculosis I must point to some important facts which relate to the staining of some of the individual anatomical elements of the tuberculous tissues, and to which I will have occasion to refer when discussing in the following pages my observations on the nature and origin of the bacillus tuberculosis.

At present it appears to be generally known that in the different individual anatomical elements, of which all animal tissues are composed, there exists a considerable difference in the capacity of absorbing coloring matters, such as carmine, hæmatoxylin, etc.; it is thus that the protoplasm of the nuclei absorbs the coloring matter of a staining fluid more readily than that of the cells themselves. This difference in the degree of absorbing coloring materials may also be observed when a tissue passes from a normal into a pathological condition, a phenomenon to which I have already referred several years ago. Thus the protoplasm of an animal cell or that of its nucleus will absorb and retain the coloring material much better when in a state of irritation

than when in its normal condition. The same may be said of neoplastic cells absorbing better than the normal cells of old tissues; accordingly in staining a section of a cancerous organ the cancer cells will be found more highly stained than those of the neighbouring healthy tissue. Pathological products, such as fibrinous exudates, the albuminous cylinders met with in the urine of cases of parenchymatous nephritis, etc., also absorb coloring matter in a high degree. In staining with aniline colors vegetable or animal tissues, similar differences are observed in the anatomical elements of these tissues, not only in the degree of power for absorbing the colors, but moreover in that for retaining them. Such an instance we observe in the staining of tuberculous tissues in which the vegetable organisms, the bacteria, retain one aniline color if once thoroughly absorbed better than the animal tissues against a second color subsequently presented to them, while the latter on their part possess a greater power of absorption. Next to the bacteria, it is the nuclei of the tubercle cells which hold the aniline color, once absorbed, against the action of the nitric acid solution, or formic acid, alcohol, etc., as well as against a second color presented to them. This phenomenon manifested by the nuclei of the neoplastic tubercle cells is so constantly observed in sections of tuberculous tissues as to become a reliable test between these nuclei and those of the neighboring normal cells. This difference in the power of retaining the aniline color, however, is not only observed to exist between the nuclei of the tubercle and those of the normal cells, but, moreover, between the nuclei of the individual tubercle cells themselves. In a section of a tubercle, stained with magenta, and discolored with nitric acid solu-

tion or formic acid, therefore, a number of nuclei will always be observed to have more or less retained the magenta, while others have lost it. The retention of the staining material by these nuclei indicates the state of irritation which generally precedes that of degeneration. As soon, however, as the nuclei commence to degenerate, their absorbing power diminishes in a degree corresponding to that of the degenerating process, to be lost entirely with the final disintegration of the nuclear protoplasm.

Although the nuclei of the tubercle cells, when in a state of irritation, hold the magenta which they have absorbed against the action of the nitric acid solution, formic acid, etc., they never do it in the same degree as the bacilli tuberculosis. This is readily seen by comparing the particular tint of the magenta which the nuclei present with that of the bacilli tuberculosis; for while the latter, when thoroughly stained and examined microscopically with a daylight illumination, present a distinct purplish color, the former appear not only paler but also, of a more reddish tint.

The foregoing remarks concerning the capacity of the nuclei of the tubercle cells to hold, when in a certain condition, the magenta absorbed against the action of nitric or formic acid, I have principally made for directing already in this place the attention of the reader to these facts upon which, as I shall show hereafter, the interpretation of certain phenomena relating to the origin and nature of the bacillus tuberculosis in human organs is based.

III.

THE MORPHOLOGICAL CHARACTERS OF THE BACILLUS TUBERCULOSIS.

In order to fully understand my observations regarding the origin and the development of the so-called bacillus tuberculosis met with in human organs and its relationship to the tubercles, the reader should be familiar with the morphological character of this organism, such as they have appeared to me in the course of my microscopical investigations.

In the study of the morphological characters of the bacillus tuberculosis it is important that these organisms should not be obscured by the substance in which they are found embedded. For this reason thoroughly stained specimens of tuberculosis expectoration containing the bacilli are preferable to sections of tuberculosis lung or other organs; though these, if very thin, also answer the purpose. In examining such a specimen of sputum containing numerous bacilli tuberculosis it will be found that they represent shorter or longer filaments which are distinctly composed of minute granules (fig. 1, *a* and *b*). The number of the latter being proportionate to the length of the filament, ranges from two to six, seldom more. While some of these filaments are straight, others, perhaps the greater number, appear slightly curved, presenting in many instances one or two angular bends. In examining, especially on the longer filaments, these curves and bends a little more closely, it will be found that in most instances they occur between two neighboring pairs of granules, suggesting the idea that the whole filament is composed of pairs of granules or diplococci (Billroth). In some instances the original building up of the filaments by diplococci is very striking (fig. 1) and cannot be mistaken. The same angular bends may

even be observed on some of the shorter filaments composed only of two diplococci; sometimes even one diplococcus appears to overlap the other (fig. 1, *b*). These angular bends appear to indicate the place where two diplococci have formed a junction by mutual attraction.

Now as regards this apparent building up of the filaments of the bacillus tuberculosis by so-called diplococci, we may point to the fact that all sphero-bacteria or micrococci, such as they are met with in various natural liquids, are artificial infusions when they appear in the form of filaments, are in the same manner built up of pairs of minute cells. Generally these filaments are formed of only two diplococci, comprising two granules; not infrequently, however, the latter by joining one another give rise to shorter or longer chains, of which they themselves represent the individual joints. The building up of these chains by micrococcus filaments and of the latter by diplococci may be easily observed in that form of bacteria generally met with in urine (fig. 2, *a*).

In many specimens of tuberculous expectoration (fig. 1, *a*), but particularly in sections of tubercles undergoing the cheesy metamorphosis or so-called coagulation necrosis (figs. 4, 5, 8 and 9), the bacillus tuberculosis presents itself in the form of groups composed of a larger or smaller number of filaments, which, differing in length, frequently overlie one another in different directions. This peculiar grouping has been mentioned by other authors, but to the extent of my knowledge none of them have ever offered a satisfactory explanation for this phenomenon. As the manner in which these groups of bacilli tuberculosis are formed stands in a certain relation with other facts elicited in my investigations, I shall postpone the remarks which I have to make on this subject to another part of the treatise.

The particular appearance which these minute cells, composing the filaments of the bacilli tuberculosis, present to the eye of the observer, differs, as I have observed, with the degree of intensity of their staining. Thus, if they are highly stained, they will appear to adhere closely to, or be fused with, one another more than is in reality the case. Such an appearance may be caused by a surplus of aniline color deposited in the constrictions existing between the individual cells. For this reason it is quite essential for an accurate study of this mutual relationship of these minute cells or granules, that they should be only moderately stained, as represented in fig. 1, *b*, and, moreover, with a suitable transparent staining material; besides, they should not be too much covered by the purulent matter of the expectoration or by the substance of the tubercles. Examined under such favorable circumstances, then, these granules will hardly ever be found completely fused or exhibiting the straight outlines of a so-called "rod;" even those which form diplococci do not appear completely fused with one another, but in all instances still show their original spherical form, separated by a more or less distinct constriction. The individual diplococci, forming the filament, however, generally appear not fused into one another (fig. 1, *b*.) A close examination of these minute granules will, furthermore, show that they do not all present one and the same diameter; on the contrary, whilst some of them appear slightly larger than the mean diameter, amounting to about 1-1500 mm., others are smaller. The latter very probably represent young cells or granules, formed by the division of larger ones. It is thus that the smallest cells are always observed at one of the ends of the filaments, where, in many instances, instead of a two-celled diplococcus, three cells will be met with. In some filaments, on the other hand, one of the

terminal cells may be seen slightly enlarged and presenting a more oval form. This enlargement and change of form precedes, as I presume, the act of division, and therefore cannot be looked upon as an approach to the bacillus form of a bacterium. In fact, among the many thousands of these filaments which I have closely examined, I have never been able to discover a single one without constrictions, that is, representing the rod-like form of a true bacillus. On the contrary, in every instance, even in those filaments in which the minute cells or granules appear as if fused, I have succeeded in dissolving the minute spherical bodies of which they were originally composed. Examined with my Tolles' homogeneous immersion objective, illuminated with very oblique light, the outlines of these granules are distinctly seen projecting in bas-relief from the filaments.

The facts which I have stated above show, then, that the bacillus tuberculosis, such as it is met with in the human lungs, or other organs, does not present the slightest trace of the bacillus form of a bacterium. A true bacillus, according to Cohn's definition, represents, as I have stated before, a rod without constrictions. Whenever a bacillus divides, the divisions are rectangular, and not preceded by a constriction of the part where the division is to take place. The bacillus subtilis, or hay bacillus, represents a fair type of the bacillus form. This organism is easily obtained from a decoction of hay. In staining a drop of this decoction upon the cover glass with a solution of methyl violet, the bacilli, contained in the former, will readily absorb the aniline color from the liquid, and then show very distinctly the rectangular divisions, which in unstained specimens appear very faintly. It will, furthermore, be found that these marks of division greatly differ from the constrictions which the bacillus tuberculosis represents. Koch

has, as far as I know, never mentioned these constrictions and the head-like character or torula-form of his bacillus tuberculosis. On the contrary, he describes the latter as a minute rod (Stäbchen), and, accordingly, regards it as belonging to that group of bacteria formed by the bacilli. The fact of the bacillus tuberculosis being composed of minute granules was first pointed out by Gibbes, several months after Koch's announcement of his discovery. Taking, therefore, into consideration the disadvantages attending Koch's original mode of staining with his alkaline fluid, of which I have spoken before, I am not disinclined to believe that when he first discovered these filaments he was unaware of their torula-form character; if otherwise, I could not comprehend for what special reason he applied the designation "bacillus" to these torula-form organisms, unless he places this designation upon the presence of spores which he stated to have discovered within the filaments. In mentioning these spores in his first paper on the subject, he expresses himself as follows:* "Under certain circumstances, to be mentioned hereafter, the bacilli form already in the animal body spores, of which the individual bacilli contain several, mostly from 2 to 4; they are oval in form and distributed at equal distances throughout the length of the bacillus."

As far as I can understand these words, they imply that the bacillus, throughout the length of which the spores are distributed at equal distances, represents a rod, and not a row of minute cells. Or did Koch, when placing the organism which he discovered in the tuberculous tissue among the bacilli, perhaps regard the individual minute cells or granules forming the filaments as individual joints of the bacillus? The spore then should be contained in these spherical joints. Or

* Berliner Klinische Wochenschrift, April 10th, 1882, p. 222.

again, are the minute cells themselves regarded as the spores? If so, then I may repeat the question which I have asked once before: Where is the body of the bacillus? For though it is possible that these minute cells, forming the filament, called "bacillus tuberculosis," may, like other micrococcus forms of bacteria, possess a gelatinous envelope, I have never seen them enclosed in a distinct sheath which might represent the wall of the original bacillus. Besides, these cells or granules are mostly spherical, and not oval, as Koch describes his spores; and, moreover, if they represented the spores, then, as there are not special rods to be seen, it would appear as if the bacillus tuberculosis were constantly sporing. Hence, there remains nothing else to presume but that the oval spores mentioned by Koch should be contained in the minute cells of the filament.

Ever since I have become familiar with the veritable bacillus tuberculosis, of Koch, I have sought in vain in various treatises written on this subject for a clear, definite description of the spores, as well as of the bacillus-rod containing them. To the extent of my knowledge there are only a few authors, who have themselves practically investigated the subject under discussion who have mentioned these spores. On account of certain discrepancies existing in their descriptions, as well as for the wants of clearness of expression, however, I have failed to derive the proper satisfaction from the sources. Thus, for instance, Watson Cheyne, who has investigated the nature of the bacillus tuberculosis on an extensive scale, expresses himself as follows*: "The tubercle bacilli vary considerably in length, the longest being about the $\frac{1}{7000}$ inch. They are

* Watson Cheyne "Reports to the Association of the Advancement of Medicine by research on the relation of Micro-organisms to Tuberculosis." Reprinted in New York Medical Abstract, May, 1883, p. 175.

narrow (about $\frac{1}{2}$ or $\frac{1}{3}$ of their length), more or less rounded at the ends, and they generally present a sort of leaded appearance, clear spots with intermediate stained parts, the rod outside the clear spots being also stained (Plate I, Fig. 10.) The number of leads in a single rod varies from four to eight, average six. The rods are generally straight, but not uncommonly more or less covered. In tissue they are generally found singly, sometimes in pairs, united at their ends or stuck together side by side. At other times there are two or three lying across each other, the axis of all being more or less in the same direction. In cultivations they are, as a rule, shorter, and stuck together in dense masses. Perhaps their shortness is due to their being broken when spread out on the glass, but I think they are really shorter when growing slowly. (Vide examination of Koch's case of injection into the veins). According to Koch they are motionless." The foregoing quotation from Cheyne's paper represents all that this author at the time says of the morphological characters of the bacillus tuberculosis. While he says nothing of spores, he, nevertheless, mentions the leaded appearance of the organism, and, moreover, "clear spots with intermediate stained parts, the rod outside the clear spots being also stained." In considering the great extent of Cheyne's investigations into the nature of the bacillus tuberculosis, his description of the organism itself is rather meagre. Besides, his expression regarding the clear spots is somewhat obscure, for while he speaks of stained parts intermediate to the clear spots, he finishes the sentence by saying that the rod outside the clear spots is also stained. As far as I am able to understand the last part of the sentence, it is a repetition of the preceding, as otherwise these words might indicate that the stained parts "intermediate to the clear spots" were not identical with the

"rod outside the clear spots." In the above description there is nothing said to the effect that these clear spots represented the spores of the bacillus tuberculosis, though I am inclined to think that the author may have regard them as such, but not being sure of their nature, has hesitated to make any positive assertions. In the same vague manner Formad also speaks of these spores, so that it almost appears as if these authors had been trying to avoid to enter into a more definite description of these bodies.

Two other distinguished authors who also quite extensively investigated the subject under discussion are Messrs. Rabes and Cornil. In order to show certain discrepancies found in the descriptions of the spores of the bacillus tuberculosis, as rendered by different authors, I shall exhibit the view of these investigators by quoting some parts of their description of the morphological characters of the organism in question, as follows: * "They (the bacilli) consist sometimes of small homogeneous rods (batonnets), sometimes of small ovoid or rounded granules placed side by side. They are difficult to see without a coloring re-agent. Nevertheless, in sputa which contain a great number of them, when treated with a weak solution of potassa they are recognized as small hyaline and colorless rods, in which no distinct granules are seen. These small rods then appear larger than in the preparations where they have been colored and dehydrated." A little farther on in the same paragraph the authors continue: "In examining with the No. 10 homogeneous immersion of Verick and the concentrator of Abbé a preparation of phthisical sputum, colored by Ehrlich's method, a larger or smaller number of small rods of various length and form are seen, distinctly alike in diame-

* *Rabes et Cornil.*—"Note sur les Bacilles de la Tuberculose," and "Journal de l'Anatomie et de la Physiologie normales et pathologique de l'Homme et des Animaux." Juillet, Aout, 1883, p. 456.

ter, some of them homogeneous, colored aniline red or slightly violet, the others formed throughout their whole length by small colored granules. In the sputa of one of our patients, the lungs of which were hollowed out by large cavities, a considerable quantity of bacilli was met with, about one hundred in the field of the microscope with an amplification of 500 diameters. The greater part of these small rods contained small granules placed side by side. We have left this sputa in a tube closed by a cork for three weeks. These sputa, under the influence of putrefaction, had lost their mucus consistence. The colored preparations have then shown to us that almost all the bacilli were solely composed of small colored granules; and they have appeared to us more numerous than in the sputa examined immediately after expectoration. We have drawn (see fig. 12, plate XXIV.) these bacteria left to themselves in the sputa during ten days. It can be seen that the greater part among them are composed of slightly elongated or spherical granules, arranged side by side. In examining closely one of these bacilli with the aid of the homogeneous immersion objective No. 10, and with a high ocular, the borders of the small rods, which are rectilinear and parallel, may be distinctly determined, and it is seen that the colored granules, which probably are spores, are seated in the interior of the small rod."*

*I cannot forbear to remark that it is impossible to form a correct idea of the morphological characters of the bacillus tuberculosis from those bacilli represented in figure 12, plate XXIII, to which the authors refer in their text. For although this figure is marked in their "Explanation" of the plates as magnified 1000 diameters, the bacilli are represented therein not larger than those in figure 10 on the same plate, marked as magnified only 150 diameters. The granules of the true bacillus tuberculosis when magnified 1000 diameters, present a diameter at least three times as large as represented in the above mentioned figure. The latter, therefore, has missed its purpose of illustrating the morphological characters of the bacillus tuberculosis.

Two years afterwards, in a lecture delivered by Cornil on Pulmonary Tuberculosis,* this investigator makes the following remarks: "The typical bacilli of tuberculosis, as observed in sputum and lung sections colored by Ehrlich's method, appear entirely homogeneous, or formed of small beads adhearing end to end."

"These small beads are considered the spores of bacilli more through analogy with other bacteria than by a true demonstration. We do not know, however, whether this parasite found in tubercular products be not the offspring of parents having an entirely different morphological appearance," etc.

These words are clear enough to show that at present this author also entertains some doubts as to the existence of the so-called spores of the bacillus tuberculosis, he admits even that they never had been truly demonstrated.

The best information concerning the spores of the bacillus tuberculosis which I have thus far obtained, was from a review written by Litten on the "Ætiology of Tuberculosis," by Koch, published in the "Mittheilungen aus dem Kaiserl. Gesundheitsamt." In order to render my arguments on this subject clearer to the reader, I shall quote from this condensed account on the ætiology of tuberculosis the part which treats of these spores, found on page 262 of the "Deutsche Medizinalzeitung," March 24th, 1884. It reads as follows: "A further *very important property of the tubercle bacilli is the formation of spores.*" It was Koch who first observed the appearance of shining bodies in hay-

**New Orleans Medical and Surgical Journal.*—A lecture by Dr. Cornil, Prof. of Pathological Anatomy, etc., Paris. Reported by Dr. E. Laplace. of New Orleans, Sept. 1885.

bacilli, which remain after the disintegration of the bacilli and are capable of germinating anew into bacilli. For the latter reason Cohn regarded them as the fruit-form of the bacilli, and designated them spores. Tinged with aniline colors these bacilli appear in the microscopic picture with short articulations, mostly consisting of two articles of which the single ones are darkly colored throughout, still resembling bacilli free from spores. In many articles, however, the appearance of a light spot is observed, which gradually increases in size while the colored contents of the article are more and more retracted to both ends, and while the sides are only still bounded by fine lines representing the outlines of the article. The light space in the interior of the bacillus article is *the spore*, which is not distinguished by its lustre but by its remaining free from coloring matters. The articulation, of course, does not always appear so sharply defined in opposition to one another as in the bacilli pictured by Koch upon the photograms (No. 76 of volume I). In many varieties of bacilli, as, for instance, in those of splenic fever, the articles appear closely opposed to one another and form a continuous thread which contains the uncolored spores at equal distances. The formation of spores in the tubercle bacilli takes place in the same way. The mutual connections of the latter remain preserved and they do not break up into single articles, but in each article a light body is formed so that the bacillus, after being stained, resembles a dark minute thread, interrupted by light egg-shaped places. With the use of the strongest systems and a considerable amplification, it may be ascertained that the spore containing bacillus presents, only on a smaller scale, the same picture as the spore-containing bacillus of splenic

fever. The spores are egg-shaped and bordered on their margins by a fine colored line, while their number amounts from 2 to 6 in a single bacillus. As every single spore occupies an article the number of the articles of the bacillus, that is the simple elements of which the latter is constructed, may be inferred from the number of spores. When a substance with spore-containing tubercle-bacilli is examined in a feebly refractive liquid medium the bacilli appear then provided with highly lustrous bodies; accordingly the latter cannot be vacuoles or simple empty spaces contained in the protoplasm of the bacillus, but must represent genuine spores. Upon the accompanying figures of the spore-containing tubercle-bacilli the latter, in order to represent the spores, had to be drawn larger than they in reality appeared by the respective amplification used."

If I understand the meaning of the preceding quotation correctly, Koch describes his bacillus tuberculosis as presenting the form of a true rod, in which, as the writer of the review expresses himself, "the mutual connection of the articles of which the bacillus is composed remains preserved." The rods do not "break up into single articles, but in each article a clear body is formed, so that the bacillus, when stained, resembles a minute dark thread, interrupted by light egg-shaped spaces." He furthermore states that the bacillus tuberculosis, when containing spores, presents the same picture, only on a smaller scale than the spore-containing bacillus anthracis. Now, as far as I know, and as all drawings of the latter—Koch's own "Untersuchungen ueber die *Ætiologie der Wundinfections Krankheiten*" (fig. 4, 13 and 14) included—show, the articles of this bacillus are characterized by square ends and do not repre-

sent spherical bodies. In the same manner has Koch represented in the form of a rod the bacilli he discovered in the blood of septicæmic mice as well as those he met with in the erysipelatous ear of a rabbit (l. c. figs. 1, 2, 3 and 12). This difference of form shows plainly that the bacillus tuberculosis *does not* present on a smaller scale the same picture as the bacillus anthracis.

During the whole course of my investigations into the nature of the bacillus tuberculosis I have closely examined the beaded filaments representing it, with the view of discovering the oval spores in the individual cells of the latter,—presuming, of course, that these cells represented the individual cells of the bacillus,—but my efforts made in this direction have been in vain. My examinations, as I have already stated before, were made under the most favorable circumstances,—that is, with Tolles' 1-10 homogeneous immersion objective, Abbé's illuminator, and the finest daylight that can be obtained from a clear southern sky. To these advantages, however, some one might perhaps raise the objection of my objective not being sufficiently high in magnifying power for discovering the clear oval spaces representing the spores in these minute cells. My reply to such an objection would be that the correction of this objective is so perfect as to render it capable of bearing not only the eye-piece B, but even C, without any more loss of definition than that caused by the loss of penetration attending all high eye-piecing. The amplification, however, obtained with my eye-piece B, as may be judged from my figures of the bacillus tuberculosis accompanying this paper, is more than sufficient to show any clear unstained oval spot or space in the cells of the stained filaments, if really contained

therein. A still higher amplification, without much loss of definition, I might obtain by making use of my Tolles' amplifier. But no advantage is gained in making these examinations with very high powers, for the reason that too much penetrative power is lost by the shortness of the focus of the latter to clearly distinguish the unstained spores in the interior of the minute cells of the bacillus.

Not having been able, then, to discover anything in the form of a spore in the granular filaments of the bacilli tuberculosis, met with in the tuberculous organs and sputa of man, and not feeling inclined to disregard the statements of Koch, I can only presume that the spores which this investigator describes he must have observed in those filaments of bacilli tuberculosis which he obtained by his artificial cultivations in nutritive substances, differing in their nature, of course, from the tubercular substances of the human body. That higher forms of bacteria are really obtained in this manner, has been proved by the researches of Buchner, Zopf and others.

Before closing my remarks on the morphological characters of the bacillus tuberculosis, I cannot forbear to point to the want of correspondence existing in the description of the spores of this bacillus given by different authors. In the passage which I have quoted above from the writings from Koch and Rabes and Cornil on the subject, the reader may, perhaps, already have noticed that this want of correspondence is very great; for while the former regards the granules or minute cells as individual articles of his bacillus tuberculosis in which the spores are contained in the form of *clear, unstained oval bodies*, the latter look upon the *stained cells themselves* as representing the spores, enclosed by the protoplasm of the

bacillus. In the first case *the spores do not absorb the staining material*, but remain uncolored and clear in the stained wall of the bacillus—article, in the other the minute cells—which Koch regards as composing the whole body of the bacillus,—are regarded to represent only the spores, and *to be capable of absorbing the staining material*, while the body of the rod—as far as I am able to interpret the meaning of the words of the authors—*remains unstained*.

Watson Cheyne, as may be gathered from the passage concerning the morphology of the bacillus tuberculosis, and which I have above quoted from his writings, speaks, like Koch, of *clear spots* with intermediate stained parts, but, as I have already pointed out before, obscures the meaning of his words by adding that the rod outside of the clear spots is also stained. In examining the illustrations accompanying his paper, however, it will be found that the filaments of the bacillus tuberculosis represented as magnified 2350 diameters in figure 15, do neither show “clear spots” nor “stained rods” outside of these spots.*

Although I have seen in a number of papers these spots of the bacillus tuberculosis mentioned as “clear spots” enclosed in a stained rod, I have never seen them distinctly represented among the illustrative figures accompanying some of these papers but in one instance; I refer to figures illustrating a reprint; also in the *New York Medical Record*, of a paper on “Gram’s Method of Staining applied to Pneumonic and Tuberculous Sputum,” by M. Afanassiew. Fig. 5 of this paper represents some tuberculous sputum stained by Gram’s method

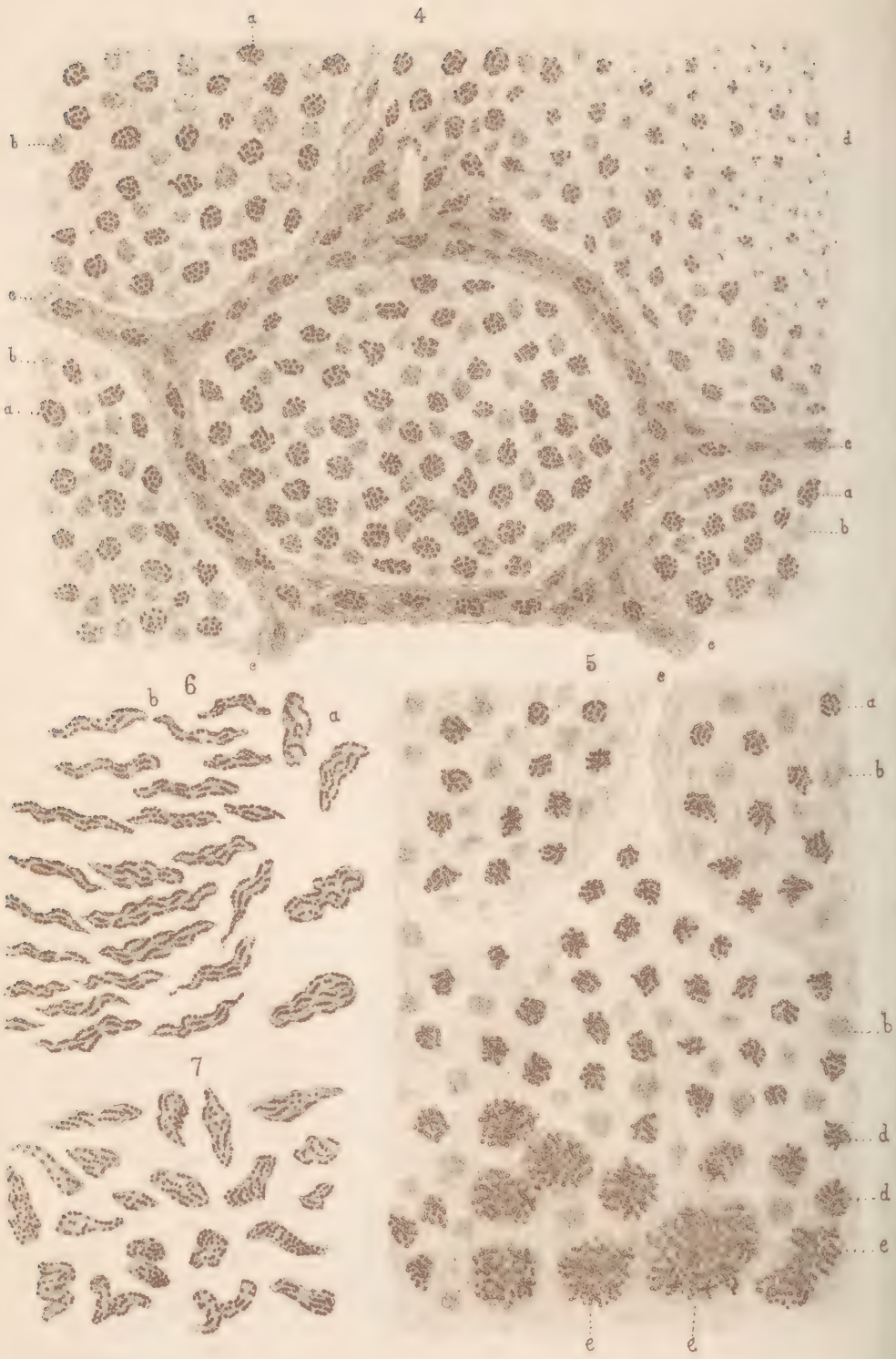
*In referring to the illustrations of Watson Cheyne’s paper, I of course take for granted that those accompanying the reprint of his paper in the “New York Medical Abstract,” and which I have before me, are correct copies of the original.

and containing numerous bacilli tuberculosis, among which several rods are observed which contain a number of clear, unstained spots or spaces in their interior. As these rods, however, are quite conspicuous among the other ordinary bacilli filaments by being of a greater thickness than these, it appears to me strange that I should never have observed them among the thousands of bacilli tuberculosis contained in the very numerous preparations of stained sputa which I have hitherto examined. But having no reason to suppose that Afanassiew drew these spore-containing rods in his paper without having actually seen them, I am almost inclined to regard them as belonging to another species of bacillus and their presence in this specimen of sputum as accidental.

Besides the discrepancies met with in different descriptions of the spores of the bacillus tuberculosis—some of which I have quoted above—there are other reasons for doubting the real existence of these spores. Thus, we might point to the comparative rarity of the presence of single granules among the hundreds of bacilli tuberculosis filaments contained in a minute portion of tuberculosis sputum or in a thin section of tuberculous lung. For if these spores did really exist in the so-called rod of the bacillus tuberculosis—it matters not whether in the form of Koch's clear, egg-shaped, *unstained* spaces or in the form of Rabes' and Cornil's *stained* granules—they would, in either case, eventually be liberated from the rod and appear among the other bacillus filaments in the form of cocci, and as, according to the views of the above named authors, each bacillus filament, or rod, either contains or represents these spores, they should be present in great numbers in each preparation of tuberculous sputum or lung. This, however, is not the case, for although some cocci forms may be observed in most preparations, they are too few in num-

ber to account for a general sporing of all the filaments contained therein.

In closing my remarks on the morphology of the bacillus tuberculosis I may, therefore, repeat that in the tissue of man, at least, I have never met with this organism in the form of a spore-containing rod, but always in the form of a filament composed of minute granules, or cells, and multiplying as it appears by a division of the latter. But as this filament represents morphologically a so called *sphero-bacterium*, I shall follow Zopf in calling it henceforth the "*bacterium tuberculosis*."



IV.

THE ORIGIN, DEVELOPMENT, DEGENERATION AND DEATH OF
THE TUBERCLE OF TUBERCULOSIS.

Although I do not intend to enlarge in this paper upon the pathological anatomy of those organs which, in the human organism, are mostly found to be affected by tuberculosis, some general remarks on this subject are nevertheless demanded, in order to serve as a basis for a thorough discussion on the relationship existing between the bacterium tuberculosis and the particular neoplasm which, in the form of small tubercles, characterize the disease.

The discovery of Villemin of tubercles artificially produced in various organs of certain animals by the inoculation of tuberculous matter, in 1866, and more particularly that of the bacillus tuberculosis by Koch, in 1882, could not but increase the interest which the medical profession has always evinced on the subject of tuberculosis, whilst it gave rise to new, and, perhaps, more thorough investigations into the

pathology of this fatal disease, than had been made before. These more recent investigations, including the labors of Villemin and Koch, into the nature and cause of tuberculosis called forth very numerous verbal and written discussions, in which the subject was thoroughly reviewed in all its aspects; so that, at the present time, almost every physician may be familiar with the history of this disease, as well as with the different theories, to which, in the course of time, it had given rise. For this reason I shall forbear making any special remark on this subject, but confine myself to only recalling to the mind of the reader that tuberculosis was formally regarded by many physicians, and still is by some, as a disease distinct from that generally known as pulmonary phthisis, catarrhal or cheesy pneumonia, etc. But although some differences may exist in the course and the accompanying clinical symptoms of these two affections of the lungs, it appears that at the present time they are by the great majority of physicians regarded as identical in their nature. My own investigations into the pathological anatomy of tuberculosis corroborate the correctness of this view, for both affections are from their beginning undoubtedly characterized by the formation of small tubercles identical in origin and structure, though in the one affection these tubercles remain confined to the lungs, whilst in the other they are also met with in other organs. Before continuing, however, our remarks on the identity of cheesy pneumonia and miliary tuberculosis, it appears to me proper to first consider the origin, development, and structure of the so-called miliary tubercle itself, as well as the different changes which it is observed to undergo during the course of the disease in question.

In order to obtain a correct idea of the particular structure

and nature of any pathological formation, it is essential that we should have some knowledge of the mode of its origin and development. Such a knowledge is particularly required in the investigation of the miliary tubercle, where the object in view is not limited to its structure and mode of origin, but, moreover, extends to the inquiring into the particular cause by which this neoplasm is called into existence. Accordingly, in commencing these investigations we must direct our attention not only to the smallest, or most recently formed tubercles, but, moreover, to every pathological change, that might be observed to have occurred in the surrounding, apparently healthy, parenchyma. Although the mode of formation of the tubercles is the same in the so-called cheesy pneumonia as in the more typical pulmonary miliary tuberculosis, the most suitable material for the microscopical study of the origin of the tubercles, will nevertheless be found in the lungs, or even other organs, of those cases affected by the last mentioned form of tuberculosis, as here, not unfrequently, portions of the respective organ are met with, in which the disease has not yet passed beyond its incipient stage. Before, however, considering the probable origin and development of the miliary tubercle, let us take a glance at the structural character which it presents when fully developed. The most suitable material for this purpose will be found in the sections, taken from lungs solely affected by miliary tuberculosis, and containing tubercles differing in size, and representing different stages of their growth.

In examining such sections under the microscope it will be seen that the miliary tubercle in the beginning of its formation appears to be limited to one alveolus, whence, however, it soon extends its growth to the adjacent alveoli

of the same terminal lobule. It is thus that most of the tubercles, met with in miliary tuberculosis, even the smallest that can be seen by the naked eye, are found to comprise a smaller or larger number of alveoli. In the formation of the larger tubercles, met with in the lungs of cases of cheesy pneumonia, the tubercular growth extends through the interstitial connective tissue to the alveoli of the neighboring terminal lobules. In this manner one of the larger lobules of the lungs, formed by a number of terminal lobules, may eventually be rendered tuberculous. The tubercular growth, however, may even extend beyond this limit and not be arrested until it has invaded a smaller or larger number of the larger lobules, giving rise to one of those tuberculous masses, or nodules, above mentioned. The formation of the larger tubercles or tubercular nodules or masses may here and there be owing to the growth and fusion of adjacent smaller ones, though my own observations have taught me that generally the tubercle of tuberculosis, whether small or large, grows from one centre in a centrifugal direction.

In examining one of the medium-sized or even larger miliary tubercles, contained in a thin section of tuberculous lung, it will be found to be composed of different kinds of cells and other anatomical elements. Whilst its main bulk, including the centre, consists of the regular tubercle cells, averaging in diameter about 1.75 mm., and of an irregular, though epithelioid form, probably produced by their mutual pressure, the cells, observed at its periphery, are smaller in size, resembling rather in form and character the so-called lymphoid or exudation cells. In many tubercles, and imbedded between the regular tubercle-cells, a limited number of cells are met with, distinguished by their unusually large size. These are the so

called giant-cells of the tubercle, *apparently* consisting of large masses of protoplasm containing numerous nuclei.

In addition to the cells thus described, however, there is another kind met with, especially in the larger and older tubercles, to which I have already referred in the beginning of this paper. They are best made visible by treating a thin section of tuberculous tissue with a solution of caustic potassa of a strength from 10 to 30 per cent., by the reaction of which all the anatomical elements contained in the section are rendered clear, and eventually destroyed, with the exception of the elastic tissue fibres and these peculiar cells. The latter then appear round or oval in form, mostly larger than the regular epithelioid tubercle cells, and always filled with larger and smaller fat globules. In many tubercles, however, these cells present a dirty brownish or blackish appearance, produced by a smaller or larger number of black pigment granules and minute fat crystals which they contain in addition to the fat globules.

Besides the above-mentioned cellular elements, many of the larger miliary tubercles contain not only the original elastic tissue fibres of the inter-alveolar septa, but, moreover, a connective tissue network, or reticulum, which is regarded by some authors as the stroma of the tubercular neoplasm.

In order to properly understand the relationship in which these different elements, composing the miliary tubercle, stand to one another, it is essential to ascertain the sources from which they are derived. This, however, is a task more difficult to accomplish than one might at first glance imagine. It is for this reason that, though this subject has been quite extensively investigated, some differences of

opinion concerning the true origin of the tubercle of tuberculosis still exist among pathological anatomists. The best mode of ascertaining the true sources of these elements consists, of course, as I have already pointed out above, in closely studying the first pathological changes taking place in the intertubercular parenchyma of the lungs, which generally manifest themselves in a multiplication of the cells of one or the other anatomical element. From these primarily formed cells, then, the further development of the tubercle may be pursued and studied in specimens exhibiting the different stages of its growth.

In examining a thin section of miliary tuberculous lung the first signs of the formation of a tubercle may be recognized in a protuberance arising from the wall of one or the other alveolus. From this protuberance the young tubercle is observed to bud, in the form of a little round or conical tumor, into the cavity of the respective alveolus. Generally, the base from which the little tumor arises, exceeds in dimension the tumor itself, but not unfrequently the latter may also be observed to be attached to the wall of the alveolus by a contracted part, or so-called neck. By a continued growth the neoplasm eventually fills up the whole cavity of the alveolus. In most instances, the growth of the base of the tubercle extending over the wall of the alveolus exceeds in activity that of its summit, in consequence of which the tubercle becomes eventually attached to the whole wall of the alveolus, thus completely filling its cavity. Not unfrequently, however, though filling up the cavity of the alveolus, it is observed to arise from a smaller base, and with a part of its body detached from the rest of the alveolar wall. In the examination of thin sections of

tuberculous lung, not only tubercles partially detached from the wall of the alveolus, but also others, having apparently no connection at all with the latter, are frequently observed. In the latter cases, this entire want of connection between the tubercle and its alveolar wall is easily explained by presuming that during the making of the section the knife passed through the detached portion of the body of the tubercle. As the miliary tubercle grows in a centrifugal direction the particular mode of its origin with the different stages of its development or growth are, of course, best exhibited at the periphery of the tubercle.

But not only in sections taken from lungs of cases of miliary tuberculosis, the particular mode and origin of development of the tubercle is observed to take place in the manner I have described above, for the same is also observed in the growth of those tubercular nodules or masses met with in the lungs of cases of chronic tuberculosis or so-called cheesy pneumonia. In sections taken from such lungs, the young tubercles are likewise seen to arise from the walls of the alveoli, bordering the nodule or tubercular mass, or from those bordering the smaller or even larger bronchioles, where they arise in the form of nipple-shaped buds. In examining attentively the borders of these tubercular masses, some inter-alveolar septa are almost always met with that are distinguished by spindle-shaped enlargements, projecting into their respective adjacent alveolar cavities, and resembling the minute miliary tubercles surrounding the small arteries, or arterioles of the pia mater in tuberculosis of this membrane. In some instances, a tubercular bud is already seen to arise from one side of the enlargement, and to project into its alveolar cavity; in others again,

a tubercle is seen to arise upon a moderately extended base from the walls of one or the other alveolus, and to extend into the infundibular cavity which is the more or less filled up by the neoplastic growth. Sometimes, even, I have observed the tubercle to extend through the infundibulum into an adjacent alveolus. When during the cutting of the section of such a tuberculous lung, the knife passes in a transverse, or even slightly oblique direction, through one of these tuberculous polypi, the section of the latter will, of course, be found to lie free in the cavity of its respective alveolus. Thus it happens that in the immediate neighborhood of these tubercular masses sections of small tubercles, distinctly composed of epithelioid cells, and in no way attached to the walls of their alveoli, are not unfrequently met with. As the diameter of these sections of minute tubercles hardly ever reaches that of the alveoli in which they lie, but on the contrary is mostly considerably smaller than the latter—in some instances not more than one-third—there will be always left a smaller or larger empty space between their borders and the alveolar walls. This circumstance, together with their being composed of distinct epithelioid cells, make them resemble minute masses of desquamated epithelium, such as are asserted by some authors to be present in the alveoli of the lungs in cases of the so-called catarrhal pneumonia, the supposed forerunner of pulmonary phthisis. I hesitate not to confess that when I first beheld these bodies I was, myself, inclined to regard them as accumulations of such desquamated epithelial cells, until closer investigation showed me their tubercular origin. In other instances, however, similar minute aggregations of these epithelioid cells may be observed to be attached to the alveo-

lar wall by short and quite narrow pedicles, resembling minute tubercles arising from the epithelium of the alveolus. To these I shall refer again hereafter.

In the foregoing paper I have described the forms in which the miliary tubercles are first seen to arise from the internal surfaces of the walls of the alveoli, but omitted to mention the particular anatomical element directly concerned in their production; in other words, whether they owe their origin to the connective tissue cells of the vessels ramifying between or in the alveolar walls, or may be regarded as a proliferation of the epithelial cells lining the alveoli. As regards this subject, some difference of opinion appears still to exist among pathological anatomists, for while some of them regard the tubercle as a product of inflammation, that is, arising from the cells of some connective tissue, or even from cells migrated from the blood or lymph into the walls of the alveoli, others regard them as a product of the epithelium lining the pulmonary air vesicles. In considering the epithelioid form of these cells, composing the greater part of the miliary tubercle, it appears at first sight difficult to ascertain the true histological origin of the latter. The difficulties met with in the investigation of this subject, however, will be found to diminish and to finally disappear, if our microscopical examinations are sufficiently thorough, and made on a great number of preparations, in order to serve as a reliable basis for sound inductive reasoning. The best way of forming a correct idea of the relationship existing between the different tubercle cells, that is, between those derived from the connective tissue-cells of the vessels, and the others derived from the epithelium of the alveoli, certainly consists in taking into proper consideration their

origin in those primary cellular layers of the germ, or blastodermic vesicle, from which the different tissues of the embryo take their start. Let us pursue, therefore, this course, and briefly review the development of the human lungs, more especially that of their parenchyma, such as it is observed in the earliest stages of embryonic life.

The *blastoderma*, or blastodermic vesicle, is formed as we know from those cells resulting from the segmentation of the yolk of the egg, which spread themselves in the form of a single layer over the internal surface of the egg-membrane, the *zona pellucida*. At a certain part of this layer, however, an accumulation of these cells in the form of an hour-glass-shaped disk, representing the so-called "*germinal area*" (*area generativa*), has taken place, in which the embryo originates. The next phenomenon observed in the development of the latter is the separation of the *blastoderma* into two distinct layers, which may be regarded as the first act of differentiation taking place, for the reason that from the outermost of these layers, called the *ectoderma*, all organs performing the functions of animal life will be formed, while the innermost, the *entoderma*, give origin to all organs destined to perform the functions of vegetative life. Besides this difference of function, however, already at this early period of embryonic life, other differences have been observed to exist, not only in the size, form and general appearance of the cells of these blastodermic layers, but, moreover, in some of their physical properties; for while the cells of the *ectoderma* are small, clear and smooth, and absorb but feebly coloring matter, such as carmine, those of the *entoderma* are larger and darker, fewer in number, filled with minute granules, and absorbing the carmine quite intensely; besides, they are rendered darker by the reaction to osmic acid than the ectoderm-cells on account of the minute fat-globules which

they contain. This difference of degree in the absorption of coloring matter, or in the reaction to osmic acid is, according to *Haeckel*, already observed in the first pairs of cells, resulting from the cleavage of the ovum.* As soon as the first morphological changes, indicating the formation of the embryo, take place in these germinal layers, another layer appears between them. This is the *mesoderma*, or so-called "motor and germinative" layer, from which all the parts of the body consisting of connective tissue, muscles and nerves, together with the urinary and generative organs are formed. During the primary stage of development of the embryo, however, the *mesoderma*, also, splits up into two subordinate layers, the outermost of which, the *lamina inodermalis* (*Haeckel*) is destined for the formation of the corium, muscles of the trunk and extremities, and the bones, while the innermost, the *lamina inogastralis* (*Haeckel*) gives origin to the muscles and fibrous coats of the intestines and their glands, the muscles of the pharynx, œsophagus, stomach and other appendages of the alimentary canals, as well as to the heart and the most important blood vessels. The divisions of the *mesoderma* may be regarded as another act of differentiation concerning the functions of those organs for which its two layers are destined, *i. e.*, the one for organs of animal, the other for organs of vegetative life. Thus the original *blastoderma* now consists of four distinct layers, which, counted from the outside, have been denominated by *Haeckel* as follows: 1. *Lamina neurodermalis* (*ectoderma*); 2. *Lamina inodermalis*; 3. *Lamina inogastralis* (*mesoderma*); 4. *Lamina mycogastralis* (*enteroderma*).

As regards the origin of the *mesoderma*, however, differ-

* H. E. *Haeckel*.—" *Anthropogenie oder Entwicklungsgeschichte des Menschen*." 3rd edition, p. 172.

ences of opinion exist among the different investigators of this subject, and the question is, as yet, not decided, whether the middle layer is derived from *ecto-* or *entoderma*, or whether its subordinate layers may not be derived from both, that is, the outermost from the *ectoderma*, and the innermost from the *entoderma*. For certain reasons, I am inclined to give preference to the statements and views of A. Koelliker,* one of the oldest and most reliable investigators, who regards the *mesoderma* as being derived from the *ectoderma* alone.

Having by the above review of the formation of the primary cellular layers of the embryo now obtained a basis upon which to rest our arguments concerning the origin and significance of the different kinds of cells of which the miliary tubercle is composed, we may turn our attention to the origin and development of the lungs, representing those organs in which the tubercle is most frequently met with. In the embryo the lungs are found to originate in the upper part of its primary alimentary canal, called the "foregut," where they first appear in the form of a minute dilatation, which, by gradually lengthening, assumes the form of a tube which, in its turn, gives rise to two similar tubular processes. While the latter represent the primary larger bronchi, the parent tube represents the trachea. From each of these primary bronchi, then, two other subordinate bronchi originate which, again, in their turn, give rise to other subordinate branches, until, by the continued formation of new and smaller ones, the whole bronchial system is eventually developed. The primary alimentary canal, from which the trachea and bronchi take their origin, is composed, as we know, of two blastodermic layers, viz.: the *entoderma*, and the inner division of the *mesoderma*, the

* A. Koelliker.—"Entwicklungsgeschichte des Menschen und der höheren Thiere." 2d edition, p. 268.

lamina inogastralis of which the former is represented by the epithelium and the latter by the fibrous envelope of the canal. These same layers, of course, build up the trachea and bronchi. According to Koelliker, however, in the beginning of the development of the bronchial system, the *entoderm*a alone takes part in the formation of the bronchial branches, which bud, so to say, into the surrounding cellular mass of the *lamina inogastralis*. This phenomenon seems to indicate that the development of the bronchial system mainly proceeds from the *entoderm*a. Soon after, of course, the *lamina inogastralis* also takes part in the process of formation of the bronchial ramifications, so that each new bud, arising from the end of its predecessor, consists already of two membranes; though, even now, the epithelium of the bronchial tubes still takes the lead in the formation of new buds. By the successive formation of new subordinate bronchial tubules the whole bronchial system appears developed at the sixth month. During the development of the latter the newly formed bronchial tubules present at their ends spherical dilatations, designated by Koelliker "*primitive gland-vesicles*," and from which, in turn, the new bronchial buds arise, but which as yet do not represent the pulmonary air vesicles or alveoli of the fully developed lungs. Already in the fourth month, Koelliker found all the bronchial tubules, with the exception of their vesicular terminations, lined by a ciliated epithelium. In the sixth month, finally, the alveoli are formed in the manner that the vesicular buds, arising from the last-formed primitive gland-vesicles do not separate any more from one another during their growth into pedunculated vesicles, but remain connected to one another, opening besides into a common space which represents the so-called "*infundibulum*." These terminal vesicles are, furthermore, distinguished by a flat pavement-like epithelium.

The above sketch which I have drawn of the development of the lungs in the earlier stages of embryonic life, shows that, while the greater part of these organs, comprising the fibrous and muscular elements of the larger and smaller bronchi, together with the walls of the alveoli, as well as the larger and smaller blood vessels, are derived from the *mesoderma*, which itself is a product of the original "animal layer" of the blastodermic vesicle, the *ectoderma*—the remaining part consisting only of the epithelia of the bronchi and alveoli may be traced back to the "vegetative layer," the *entoderma*. But as the miliary tubercle is found to be built up chiefly by comparatively large cells, epithelioid in form, it would almost appear to be a product of the epithelial cells lining the alveoli. This, however, is not the case, for, though these tubercle cells do, to a certain extent, resemble in form those of an epithelium, they, nevertheless, as we shall see directly, are derived from another source. But even if we should fail to trace them back to another tissue than the alveolar epithelium, we might point to a certain phenomenon, observed in the life history of the miliary tubercle, which clearly shows that this neoplasm cannot be the product of an epithelium. I refer to the phenomenon observed in those cases of so-called "fibrous miliary tubercles," in which the tubercle cells become organized into a tissue of a higher grade, into a sort of connective, or so-called "cicatrical tissue." This process of organization, as we know, is never observed to take place in the cells of an epithelium, or in those of a gland, but, on the contrary, always involves the cells of connective tissues, or their descendants. Nor is it limited to cases of fibrous tubercles, for, in those indurated portions of lungs of cases of chronic tuberculosis, also, tubercle cells may be seen to elongate and to be converted into a sort of coarse connective tissue.

The best example, however, for showing that the miliary tubercle is not a product of an epithelium, are those tubercles met with in the peritoneal layers of the mesentery and intestines, but still more those which are formed around the small blood vessels of the pia mater. More than four years ago, I made a number of examinations of the tubercles surrounding the blood vessels of this membrane, and distinctly saw them arise from the connective tissue cells of their adventitia. Some of these vessels were so minute, that, though they were stained with picro-carmine, it was difficult to distinguish them by the unaided eye. Suspecting at first the tubercles to arise from the endothelium of these vessels, I directed my special attention to this layer, the cells of which were easily distinguished in the smaller arterioles, but failed in my expectations, as I found, in every instance examined, the endothelium entirely free from tubercle cells, while in the adventitia they were met with in all stages of development. Arising from the cells of the adventitia of the arterioles, or even from the nuclei of the capillary vessels—which generally are also surrounded by a thin layer of cell protoplasm—the tubercle cells multiply by division, and form tubercles too minute to be seen by the naked eye. Though of a moderate diameter, when first arising from the connective tissue cells of the adventitia, they soon enlarge, until they have attained the diameter of those cells, composing a fully developed tubercle, while by mutual pressure they are rendered polygonal in shape resembling then the cells of an epithelium. It must not be overlooked, however, that there are many tubercle-cells, which present very irregular forms, without resembling in any point a regular epithelial cell. The minute tubercles, when first formed, are observed to rest upon the wall of the vessel in the form of minute irregularly shaped masses, though by

continued growth they finally surround it, and assume that ovoid form characteristic of the tubercles of these vessels. The diameter of these tubercles, when fully grown, are generally proportionate to those of the individual vessels upon which they are found. The miliary tubercles met with in the peritoneal layers of the mesentery must, as there exists no epithelium in their close vicinity, of course, arise from the cells of some connective tissue, or, perhaps, as Rindfleisch states, from the endothelium of the lymphatics, or blood vessels. As regards the tubercles of the small intestines I may state, that I have endeavored to trace the connection of these tubercles by carefully separating under water, and with the aid of a strong loupe, the different layers of the intestines. In a number of instances I found the little tumor arising from the fibrous, and extending through the muscular coat. In others, however, as may also be seen in thin vertical sections of the intestines passing through the tubercle, the latter involved the fibrous layer of the mucous membrane where it may finally by its degeneration give rise to tuberculous ulceration. In examining a small miliary tubercle of the liver, the tubercle cells were also seen to arise from the cells of the minute blood vessels, though I would, for the present, not positively assert, that the hepatic cells take no active part in the formation of the tubercle. The same appears to be the case in the kidneys, though in these organs I have, in some instances, met with glomeruli, the vessels and also the capsules which presented the appearance of having been transformed into a sort of connective tissue.

In studying the mode of the peripheral growth and extension of the tubercles in thin sections of tuberculous lung, it will be observed that it always takes place along the adjacent alveolar septa, which are thickened by the multiplication of

of smaller or larger tubercle cells arising from the connective tissue cells of the adventitia, or, perhaps also, from the cells of the endothelium of the vessels, ramifying in these septa. It is thus that in these sections the outlines of the tubercles, when examined under the microscope, appear but rarely as evenly curved lines, though to the naked eye the little round or oval tumors may present a smooth appearance. In most instances, the borders of the miliary tubercles are irregular, to a certain extent star-shaped, or multipolar, the processes being formed by the adjacent inter-alveolar septa, along which the growth of the tubercle proceeds. This is especially the case in those large tubercles and tuberculous masses, met with in those lungs affected with chronic tuberculosis, in which the mode of extension of the tubercular process may be studied to advantage.

After having in the preceding paragraphs endeavored to show that the tubercle cells are most probably derived from the connective tissue cells of the adventitia of the vessels, ramifying in the inter-alveolar septa of the lungs, I shall now pass over to a brief consideration of the general character and relations of all the cells met with in the anatomical composition of the miliary tubercle. Presuming, then, from what has been said above, that the true tubercle-cells are descendants of connective tissue cells, it still remains for us to determine the origin of the other kinds found in their company. In considering first the origin and signification of those small lymphoid cells, generally met with along the periphery of the tubercle, we may suggest that they represent true exudation cells, or, in other words, colorless blood corpuscles, emigrated from the neighboring congested blood-vessels; or, as they are not met with in the main body of the tubercle, they might also be regarded as young tubercle-cells, derived, like the others, from connective-tissue cells. In most instances, the neighboring

blood-vessels of the miliary tubercles are found congested, and, if this is not the case, it may safely be presumed that they were congested during, and even previous to the formation of the tubercles; for it can hardly be supposed that the tuberculous process would take place and continue without an increased activity of the minute blood-vessels, giving rise to a morbid irritation of the connective tissue cells of their adventitia. The abnormal activity of these vessels, however, would soon be followed by a relaxation of their walls, causing a retardation of the blood-current within them, which would finally lead to a permanent congestion of these vessels. Under these circumstances it is not improbable that a number of colorless blood corpuscles emigrate from the blood-vessels, and in association with the tubercle cells—which at the same time are formed from the irritated and now multiplying connective tissue cells of the adventitia—take their part in the formation of the tubercle. It is thus that these lymphoid cells are always met with at the periphery of the tubercle, or in the alveolar septa.

The next kind of cells to be considered are the so-called “giant cells” which, greatly differing among themselves in their diameter, and individually containing a smaller or larger number of nuclei, are principally met with in the older and larger tubercles. Although surrounded by the general mass of tubercle cells they remain unconnected with the latter. In thin sections of tubercles, they appear finely granular, mostly round or oval, though sometimes irregular in form; they are surrounded by an empty space which separates them from the regular tubercle cells, though, in some instances, they appear connected to the latter by processes arising from their body. Although these giant-cells have frequently been the subject of special study, pathological

anatomists still differ in their views as to the origin, nature and signification of these formations. By some they have been regarded as representing coagula within the bloodvessels, around which the tubercle is developed, their nuclei being partly derived from the colorless blood corpuscles of the coagulum, partly from the endothelial cells of the vessels; or, also, the whole giant cell representing a conglomeration of colorless blood-corpuscles;—while on the other hand they have been looked upon as conglomerations of epithelioid tubercle cells, or of epithelial alveolar cells. Again, according to another view, they are derived from the connective tissue cells, or also, from the endothelial cells of the lymph-spaces. When met with in tubercles of the testicle, liver, kidney, and mammary gland, they have been regarded as derived from the epithelia of the seminiferous tubules, hepatic ducts, uriniferous tubules, and milk ducts. Without enlarging upon the various theories existing on the origin of these giant cells, we may say, that they are generally considered to represent smaller or larger masses of protoplasm, derived either from the growth of one cell, the nucleus of which alone was subjected to the process of multiplication, or from a fusion of the protoplasm of a number of cells with single nuclei. From my own observations it appears to me that perhaps the greatest number of these giant cells are formed from coagula of blood within the blood-vessels. I have been convinced of this by observing, especially in thin sections of fibrous tubercles, a number of these cells or masses of protoplasm still to consist of a mass of brownish polygonal cells, lying loosely in, or even connected by some points of their periphery with the wall of empty spaces, representing most probably the lumina of blood-vessels. The walls of the lat-

ter, though fused with the surrounding tubercle, and, like this, consisting of long, spindle-formed cells, could be still distinguished. Whether the polygonal cells, generally surrounded by a brownish, finely granular, substance, were derived from the colorless blood-corpuscles of the coagula, or from the cells of the endothelia of the vessels, I leave for the present undecided. Generally, there were no colored blood-corpuscles observed in the mass, a circumstance, which is, however, easily explained by assuming that the protoplasm of these corpuscles had been appropriated by the other cells to serve them as nourishment during their growth, while the hæmoglobin of the former was left behind. The degeneration of the protoplasm of the giant cell thus formed, which, of course, eventually takes place, causes the obliteration of the outlines of its component cells, so that the whole formation assumes a finely granular brownish appearance. A number of giant cells presenting this appearance and containing a smaller or greater number of nuclei are, therefore, always met with in the tubercles of the same section of lung. But though, as I have said above, the greater number of giant cells may be formed in the manner just stated, I have good reasons to believe that others represent conglomerations of cells of the alveolar epithelium, which, during the growth of the tubercle, were surrounded by the multiplying cells of the latter. To this view I was chiefly led by meeting in a number of alveoli with certain conglomerations of cells, which, presenting the average size of a giant cell, resembled those cells lining the wall of the alveolus, to which they appeared to be attached. These giant cells do not present a brownish appearance, but absorb coloring matter more intensely than the surrounding tubercle cells. I have

never observed giant cells converted, like the true tubercle cells, into any form of connective tissue.

Besides the giant cells there is another kind of cells met with in the miliary tubercle, the origin of which we shall now consider. I refer to those peculiar cells, which are characterized by their brownish or blackish appearance, and by the fat globules and fat crystals they contain; they are, as before mentioned, met with in sections of older tubercles, especially when treated with a solution of caustic potassa. These cells are generally single, and mostly met with along the periphery of the tubercle. They always contain a considerable number of smaller and larger fat globules, and many of them fat crystals, and black pigment granules besides; the latter, in fact, causes their brownish or blackish appearance. By these characters they are easily distinguished from true tubercle cells; for, though many of the latter also undergo fatty degeneration, they do not contain so great a number of large fat globules as the former, nor do they contain fat crystals, or pigment granules. I doubt not but that these cells are identical with the epithelial cells lining the alveolar cavities which, during the growth of the tubercle, are surrounded by, and inclosed in the mass of growing tubercle cells, to finally undergo the fatty metamorphosis, whilst in the older tubercles the fat globules will be converted into fat crystals, or, even, into black pigment. Not unfrequently these cells are also met with in the expectoration of chronic cases of tuberculosis.

There is another anatomical element met with in many, though not in all tubercles, which like the giant-cells has frequently been a subject of discussion, or even of controversy, among different investigators. This is the so-called "reticu-

lum." As far as my own observations extend, I may state that such a reticulum, which by some authors has been compared to the stroma of some pathological tumors, appears to exist in many miliary tubercles, especially in the older ones, whilst in others it is certainly absent. For the reason, however, that I entertain some special views on the origin of this reticulum, which to explain would consume too much space in this treatise, I must for the present forbear to enlarge upon this subject and postpone its discussion to some other occasion.

In the great majority of cases of tuberculosis, the miliary tubercles or tuberculous masses undergo a certain kind of degeneration, known as "coagulation necrosis" which lead to their final destruction. Not unfrequently, however, the cells of the miliary tubercle, instead of undergoing this retrograde metamorphosis, show an inclination to become organized into a higher grade of tissue, by gradually assuming a more and more elongated form, in order to be finally converted into a sort of connective, or so-called "cicatricial tissue." This process may be observed in all its various stages in those indurated portions of lung met with in cases of chronic tuberculosis, where it involves not only the tubercle cells, but also those of the interstitial connective tissue of the organ as well as of the blood-vessels, etc. The tendency of the tubercle-cells toward organization is, moreover, and perhaps more distinctly, displayed in those cases of so-called "fibrous tubercle," the lungs of five of which I have microscopically investigated. Here, the tubercles, though miliary in character and mostly small in size, are frequently found lying very near to one another, forming smaller and larger groups or masses. Sometimes even, they fuse with another, though it can always be seen that each tubercle had developed from its own individual center. These tubercular groups, or masses, I mostly found

in the apices of the lungs; only in some instances I observed them, as also single fibrous tubercles, in the other lobes of these organs. In all cases of fibrous miliary tuberculosis that came under my notice, the tubercles were not what might be called "numerous" as we often observe in acute miliary tuberculosis, but they were almost always associated with a greater or less peri-bronchitis fibrosa, or with interstitial pneumonia (cirrhosis of the lungs), and generally characterized by an abundant formation of black pigment.

It is not often, however, that the tubercular process in the lungs is arrested by a fibrous metamorphosis of the tubercle cells; on the contrary, in the great majority of cases of tuberculosis, so already mentioned, the disease is carried to a fatal issue by a retrograde metamorphosis, the so-called "cheesy degeneration," or "coagulation necrosis," which the elements of the tubercular growth gradually undergo. By this process, which always commences in the center of the tubercle, and progresses toward its periphery, the protoplasm of the tubercle-cells appears to coagulate and to be converted into a cheesy substance, by the final disintegration and liquefaction of which a cavity is formed in the center of the tubercle. In the course of the degenerative process the outlines of these cells become obliterated, and their protoplasm is gradually converted into a cheesy granular mass, containing minute shapeless bodies or particles. These bodies, I suppose, represent to a certain extent the remains of the nuclei of the tubercle cells, which appear to possess a greater power of resistance to the pathological cause of the process than the protoplasm of the cells. The direct cause of the coagulation-necrosis of the miliary tubercle has, as yet, not been positively determined, though the degeneration is commonly ascribed to a want of nutrition due to the absence of blood-vessels in the tubercle. In exam-

ining thin sections of tuberculous tissues we already observe traces of the degenerative process in almost all tubercles; it is only the smaller ones, or those most recently formed, that are still free from degeneration. In the older and larger tubercles, small cavities, formed by the final disintegration of the cheesy mass, are observed in their center, whilst at the periphery the tubercular growth is still going on. In those large tubercles, formed by the meeting and fusion of a number of smaller ones, several centers of degeneration and disintegration may exist at the same time. By the breaking down of these tubercles a number of small cavities are formed throughout the tuberculous portion of the lung, which, in the course of the disease, may enlarge by the ulceration and final destruction of the intervening non-tuberculous parenchyma. Such a condition is mostly observed in miliary tuberculosis. In some cases of chronic tuberculosis, however, smaller or larger circumscribed cheesy masses, surrounded by healthy parenchyma, are frequently met with, in which only one cavity, produced by the breaking down of their substance is found to exist. From this circumstance it appears that in these masses, some of which are more or less spherical in form, the tubercular process started from only one center, and after having proceeded in a radiating direction to a certain extent, was by one or the other cause arrested. These formations represent, in truth, miliary tubercles on a large scale. They are, generally, partially detached, partially still connected with the surrounding healthy parenchyma. Several years ago, I have hardened quite a number of these circumscribed cheesy masses, or nodules, some of which as large as a walnut (about one and a quarter inch in diameter), in Mueller's fluid, followed by alcohol, with the view of investigating their exact nature in thin sections. The microscopical examination of these sections showed me

that, while at the borders of the cavities the substance of these giant tubercles was, as in the ordinary miliary tubercles, completely degenerated and disintegrating, their former structure could be still distinguished throughout the greater part of the section. Not only the outlines of the numerous alveoli, bronchioles, interstitial connective tissue, etc., which had been involved by the growth, but also, toward the periphery of the latter, those of the tubercle cells could still be recognized. The borders of these circumscribed masses were formed by long structureless bands, concentrically arranged around their periphery and connected with the surrounding non-tuberculous parenchyma. No traces of the outlines of elongated cells, indicating their formation from tubercle-cells, could be discovered in these bands; but though of a smooth homogeneous aspect, they rather appeared to have at one time represented bundles of neoplastic connective tissue, the product of some inflammatory process. A closer study of the subject subsequently showed me that they represented the former walls of the adjacent alveoli of the surrounding non-tuberculous parenchyma, which, being put on the stretch by the increasing dimensions of the tuberculous growth, had adapted themselves to the peripheral form of the latter, and, through the inflammatory irritation extending from the neighboring tuberculous mass to their blood-vessels, were eventually converted into bundles of a coarse neoplastic connective tissue. That this was the true explanation of the phenomenon observed, was proved by the surrounding alveolar walls of the healthy parenchyma, which, still connected to these fibrous bands, presented in the section the form of more or less elongated meshes, produced by the stretching of the lung parenchyma.

The conversion of the alveolar walls into neoplastic connective tissue, however, is not only observed around the periphery of the

above described tuberculous masses, but takes place also in other localities of tuberculous lungs, for instance, along the borders of those portions of indurated lung, met with in chronic tuberculosis. Even, along the periphery of miliary tubercles, sections of the alveolar walls of the surrounding parenchyma are frequently observed to present the form of elongated meshes. A similar aspect is presented to the eye of the observer in the microscopical examination of sections made from lungs affected with peribronchitis fibrosa. Here sections of obstructed bronchial tubes will be met with in which the original structure of their walls is entirely obliterated, and the whole tubule appears to be converted into connective tissue; the cavity seen in the center of the tubule represents the disintegrating fibrinous thrombus. The sections of such bronchioles somewhat resemble those of miliary tubercles, though a closer examination will show no trace of a tubercle cell, but rather that they consist of concentrically arranged homogeneous looking bands, some of which are still connected with the elongated alveolar walls of the neighboring parenchyma of the lungs.

Although the formation of these fibrous bands along the borders of tubercles, otherwise tuberculous portions of lungs, might be regarded as a means of nature to arrest the morbid process of tuberculosis, this is rarely the case. On the contrary, the homogenous structureless appearance of this neoplastic connective tissue already shows that it will be, like the tuberculous portions of lung which it borders, finally subjected to the coagulation necrosis. The elongated spindle shaped tubercle-cells, playing a prominent part in the process of induration of certain portions of tuberculous lung, either such as they are, or transformed into a coarse connective tissue, are in most instances likewise doomed to undergo the same destructive process. It is this that in cases of chronic tuberculosis

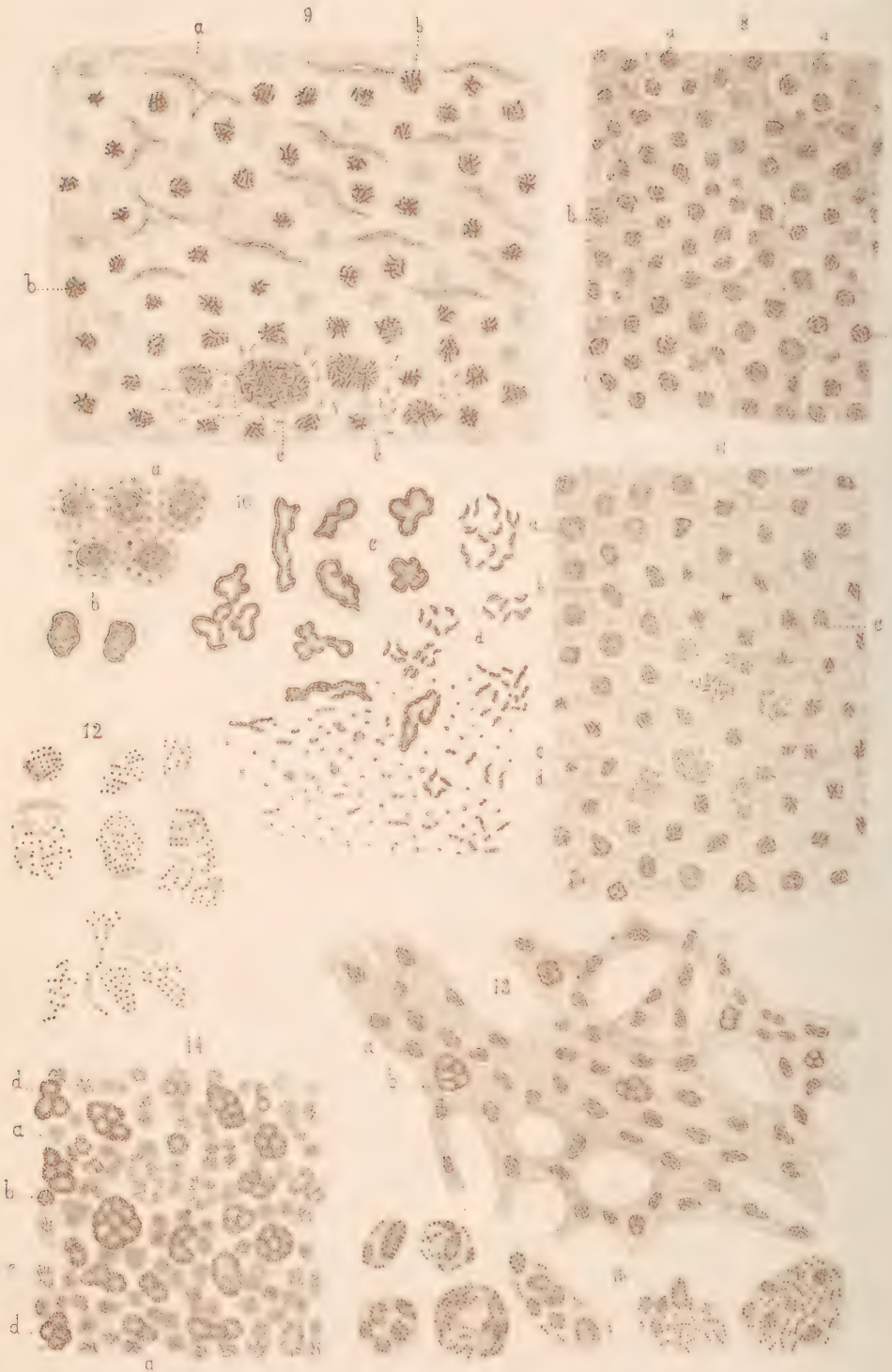
very considerable portions of lung are frequently destroyed and large cavities formed. The only organs, capable of resisting this general destruction, are the larger blood vessels and bronchial tubes, which are frequently met with stretched across these cavities in the form of single cords. Like the ordinary miliary tubercle, the fibrous tubercle, also, is subject to undergo, at least in its center, the coagulation necrosis.

From the above sketch of the origin, development, retrogression and death of the miliary tubercle in its various forms, it will be seen that the tubercular process is very complicated, and that it closely resembles in its products and their metamorphoses the process of chronic inflammation. To convince ourselves of the truth of this assertion we have but to examine and study the condition of the lungs of a case of chronic tuberculosis. In such lungs all the various stages of the inflammatory process will be found represented in different localities of these organs. Thus we may find the superior lobe hollowed by smaller or larger cavities, which, frequently communicating with one another, are like a chronic abscess lined by a so-called pyo-genetic membrane, and contain a greater or lesser quantity of purulent matter. The remaining parenchyma of the lung between these cavities is generally found indurated, and, when microscopically examined, presents to the eye of the observer a most variegated picture of its anatomical elements passing through the various stages of the inflammatory process. Approaching in our examination the base of one or the other lung we may find, according to the prevailing circumstances of the case, a decrease of the inflammatory destruction in the absence of the cavities, whilst the parenchyma, though still congested and containing large tubercles or tubercular masses, appears more soft and spongy than in the upper portion of the lung ; or, at the very base of

the organ, the parenchyma may even present the appearance of a typical miliary tuberculosis. In accordance with the special conditions of the different parts of such a lung; its surface also presents a variety of colors and their shades, for, whilst one portion of it may appear more or less gray by the induration of its parenchyma or the thickening of the pleura, another portion may by the congestion of its vessels present a red or blue appearance, while a third will exhibit all the macroscopical characters of emphysema. Thus it happens that, in severe cases of chronic tuberculosis, a combination of otherwise individual inflammatory diseases of these organs, such as bronchitis, peribronchitis, bronchiectasis, interstitial pneumonia, etc., may be found to exist at one and the same time.

With the foregoing paragraph I close the general remarks on the pathological anatomy of tuberculosis, to which I referred in the beginning of this division of the present treatise. The sketch which I have drawn of the origin, development and death of the tubercle of tuberculosis is, though it may serve my present purpose, far from being complete. But as the reader may infer, from what I have already said above, the subject of tuberculosis is too complicated and extensive for a thorough discussion in all its details in the limited space of my present treatise, requiring rather the numerous pages of a whole volume. Whatever, therefore remains to be said on the pathology of tuberculosis I will have to postpone to a more convenient occasion.





V.

THE RELATIONSHIP OF THE BACTERIUM TUBERCULOSIS TO
THE TUBERCLES OF THE HUMAN LUNGS AND OTHER
ORGANS.

The bacterium tuberculosis does not present itself in the same form, or in the same stage of development, in all portions of tuberculous lung, or even in all forms of tubercle. On the contrary, its development depends to a certain extent on the particular development, degeneration, and death of the tubercular growth. Greatest in number and highest in form of development, the organism is generally met with in tubercles which have very slowly and completely undergone the coagulation necrosis, and in which the outlines of the tubercle cells, as well as those of their nuclei, have disappeared. Such tubercles are generally met with in the lungs of cases of chronic tuberculosis. In some of these tubercles the bacteria tuberculosis are met with, embedded in the degenerated tissue, in very large numbers, whilst in others

they are not so numerous. They are always found to lie in groups of four or five, or even more individuals, in the same way as they are frequently met with in the tuberculous expectorations. The morphological characters of the bacteria contained in these tubercles are the same exhibited by those already described and met with in tuberculous sputum. In examining microscopically thin sections of tuberculous tissue, containing very numerous bacteria tuberculosis, only a certain number of them can be at one and the same time brought into focus and distinctly seen in their proper outlines; the rest, being embedded more deeply in the tissue, and out of focus, will cause the tissue itself to appear as if stained by the same color, which in reality is not the case. Although the peculiar grouping of the bacteria tuberculosis has also been observed and mentioned by other authors, I have not, as yet, met with a satisfactory explanation for this phenomenon. It appears, therefore, that it is generally regarded as a matter of fact which needs no special explanation, if we simply regard the individuals, forming one group, as the descendants of that particular bacterium which, coming from the surrounding atmosphere, first entered the lungs during the act of respiration, to settle on the very spot in one or the other alveolus, where the group is found. And I must confess that in the beginning of these investigations, I entertained to a certain extent a similar view, until I made a certain observation, which explained to me the phenomenon of the bacteria tuberculosis appearing almost always in the form of groups, when met with in the tissues of the human organism. This observation I shall now describe.

In the latter part of the spring of 1883, after I had suc-

cessfully stained the bacterium tuberculosis in tuberculous expectorations, and in numerous thin sections made from different tuberculous lungs, and, while still testing different methods of staining, I observed in sections, stained with methyl violet, and decolored by alcohol, that, though no stained bacteria could be discovered in the section, a number of nuclei had retained some of the blue color, while the rest of these bodies had given it up. At the same time, I noticed in the interior of these nuclei several granular bodies of a slightly deeper stain. Regarding these stained nuclei as having been formed more recently than those unstained, and the bodies which they contained as their ordinary, legitimate granules, I attached no particular importance to this observation. Some time afterward, however, when again examining sections, made from the lungs of a case of typical miliary tuberculosis, and stained by Gibbes' method, first with magenta and then with chrysoidine, I observed the same phenomenon, though more distinctly than before. In these sections, in which the tubercles were comparatively small, and in which no bacteria tuberculosis whatever could be discovered in their cheesy degenerated centres, I observed a number of deeply stained granules, as well as granular filaments, in the interior of the nuclei of the tubercle-cells occupying the periphery of the tubercle. Whilst these bodies, which in every respect resembled bacteria, were deeply stained by the purplish blue of the magenta, the protoplasm of the nucleus itself was stained yellow by the chrysoidine. This observation explained to me at once not only the cause of the peculiar grouping of the bacteria tuberculosis, as observed in the cheesy parts of the tubercles, but,

moreover, their true origin in the nuclei of the tubercle-cells, and also showed me the direction in which my investigations had to be further pursued. In examining other sections of the same lung, stained in the same manner, I then observed the same purplish blue bodies not only in the interior of the nuclei of the tubercle-cells, but also in the nuclei of all the cells contained in the different tissues of the bronchioles adjacent to tubercles; that is, in the nuclei of the connective tissue-cells of the mucous and fibrous coats (fig. 6 *a*) in those of the muscular fibre-cells (fig. 6 *b*) and even in those of the cartilage-cells contained in the minute cartilaginous plates of the bronchioles. I furthermore observed these bodies in the nuclei of the cells of the adventitia of some of the smaller arteries. By repeatedly observing this same phenomenon afterward in sections made from the tuberculous lungs of other cases, especially of miliary tuberculosis, I was, at last, convinced of the bacterial nature of these stained bodies within the nuclei of the bronchial walls; the more so as they were not observed in the nuclei of the walls of bronchioles not adjacent to tubercles, nor in those of the healthy parenchyma of the lungs. While these bodies were stained of a deep purple by the magenta, the protoplasm of the nuclei appeared stained more feebly by the same color, indicating that the latter were affected by some irritation, probably derived from the neighboring tubercle. In staining these sections with a second color, such as chrysoidine or Bismarck brown, it was absorbed by the protoplasm of the nuclei, while the bacteria within the latter kept their purple tint; only when exposed a comparatively long time to these second colors, the bacteria assumed a brownish tint, though much darker than that of the nuclear protoplasm.

The correctness of the observations just described, I found corroborated by the examination and study of a very considerable number of stained sections, taken not only from the lungs of cases of miliary, but also of chronic tuberculosis, and of tuberculous livers, spleens and lymphatic glands, in which the same well-stained granular bodies were always observed in the interior of the nuclei of those tubercle cells occupying the periphery of the tubercle. All that now remained to prove the bacterial nature of these bodies was to meet with such sections of tuberculous tissue in which not only the origin and development of the bacteria tuberculosis in or from the protoplasm of the nuclei, but also their liberation from the latter could be clearly demonstrated. By the close examination of numerous well stained sections of large miliary tubercles of the lungs, liver and spleen, or of such tubercles situated near the borders of the tuberculous portions of the lungs of cases of chronic tuberculosis, I succeeded, at last, in tracing in one and the same section the bacterium tuberculosis from its first appearance in the nuclei of the tubercle cells to its full development and its liberation from the degenerated nuclei in the cheesy centers of the tubercles. Specimens of tubercles in which the bacterium tuberculosis can be traced from its origin to its liberation are, for certain reasons, to be stated directly, not found in every tuberculous portion of lung, liver, etc., though they are often enough met with, especially if properly looked for, to furnish to every investigator ample opportunity to corroborate the correctness of my statements.

As far as I know from the current medical literature it has now been asserted by a number of investigators on the subject under discussion, that free bacteria tuberculosis *cannot be discovered in all tubercles*, and, moreover, that whenever

they are met with in tuberculous tissues, it is principally in that portion of tubercle, or tuberculous mass, in which the process of coagulation-necrosis is going on. My own observations not only corroborate the truth of the statements of these authors, but also enable me to furnish in the following pages the explanation for this phenomenon.

From my observations it appears that the development of the bacteria tuberculosis in the nuclei of the tubercle cells stands in a certain relationship with the degree or rapidity of the degenerative process taking place in the nuclei; in other words, the more rapid the course of the degenerative process,—not only of the nuclei but also of the protoplasm of the cells,—the smaller is the chance for the bacteria to reach their full development or maturity; whilst on the other hand, the more slowly this process proceeds, the more time will be afforded to these organisms for reaching their full development and their final liberation from the degenerated protoplasm of the nuclei.

The appearance of the bacteria in the nuclei is always preceded by a shriveling of the nuclear protoplasm, indicating that the degenerative process has commenced. The normally round outlines of the nucleus, then, become irregular, whilst its double contour appears darker and more prominent. With the advancing degeneration the irregularity of the outlines of the nucleus increases, whilst its margin, represented by the double contour, is breaking up, first into a few and then into more fragments, which are finally converted into a number of minute filaments of a granular or bead-like composition. In the course of the degenerative process the power of retaining aniline colors against decolorizing agents, such as nitric or formic acid, etc., increases in the margin of the nucleus, and in the fractions into

which it has broken up, in proportion to the degree of degeneration. It is thus that in thin sections of tuberculous tissue, stained with magenta, the irregular shriveled margins appear of a dark red, which ultimately, in the filamentous fragments changes into purple.

Whilst the above described changes are observed to take place in the protoplasm of the nuclei, that of the cells, of course, undergoes the same degeneration. Accordingly the bodies of the cells appear paler and paler, until finally their outlines can be no longer distinguished, their protoplasm having lost all power of absorbing coloring materials, and undergone the coagulation-necrosis. As far as I am able to judge, the degenerative process not only commences in the protoplasm of the cells, but runs there a more rapid course than in that of the nuclei. This is seen in examining the cheesy centres of miliary tubercles, in which no trace of the outlines of the cells can be discovered, while a number of shriveled nuclei, containing forms of more or less perfectly developed bacteria, or minute fragments of nuclei, are still met with. Judging, however, from the fact observed in these cases, that the remains of the protoplasm of these nuclei still present the yellow color of the chrysoidine, or Bismarck brown with which the section was lastly stained, whilst the bacteria show the purple of the magenta, it appears to me that the protoplasm of the nuclei never undergoes a perfect degeneration, as, otherwise, it would not have retained its capacity of absorbing coloring matters. It seems, therefore, more probable that the shriveling of the nucleus stands in some relation to the development of the bacteria, for the more fully the latter are developed, the more the nucleus shrivels; in other words, the protoplasm of the nucleus ap-

pears to be necessary and appropriated for the development and growth of the bacteria.

In referring to some of the illustrative figures, accompanying this treatise, the reader will be enabled to understand more fully my statements regarding the development of the bacteria tuberculosis in the nuclei of the tubercle cells. Let us begin with fig. 3, which represents a small part of the periphery of a miliary tubercle with several of the neighboring non-tuberculous alveoli magnified about 625 diameters. In this figure we recognize at *a* the shriveled nuclei containing more or less developed bacteria tuberculosis, at *b* the epithelial cells of the non-tuberculous alveoli, and at *c* the interalveolar septa with the nuclei of their multiplied connective tissue-cells derived from the adventitia of their vessels, etc.; *d* represents a small portion of the periphery of the tubercle, while *e* represents a young tubercle which has arisen from a part of the wall of a large alveolus, or perhaps infundibular cavity, and which, contrary to the rule generally observed, has undergone the coagulation-necrosis at the periphery of the tubercle. The cheesy centre of the tubercle is situated toward the left and outside of the drawing. In proceeding with the examination of the anatomical elements represented in this figure from the right to the left side, we observe in the non-tuberculous alveoli, on the right side, already a number of nuclei which present the degenerative changes, above described, in their different degrees. Some of these nuclei are contained in the epithelial cells, while others appear to be located in the open spaces between these cells, occupied by the capillaries. From this it appears that the development of the bacteria tuberculosis not only takes place in the nuclei of the true tubercle cells, derived from the cells of connective tissue, but

also in those belonging to the cells, lining the alveolar walls, and which descend from the cells of the entoderma. The same phenomenon is observed in the liver as we shall see hereafter. Although no trace of tubercular growth is found in these alveoli bordering the tubercle, quite a number of nuclei containing developing bacteria are nevertheless already observed in the inter-alveolar septa. The changes observed in these nuclei are most probably caused by a morbid irritation, derived and radiating from the neighboring tubercle. In passing to the left of the figure we observe at *d* the periphery of the tubercle. Here, most of the nuclei of the tubercle cells contain bacteria tuberculosis in different stages of development; the shades between these nuclei represent others out of focus. Finally at *e* we observe in the young tubercle, having already undergone the coagulation-necrosis, still a number of nuclei containing bacteria, together with others already disintegrated, the remains of which are observed throughout the cheesy mass in the form of fragmentary granular bodies. Although in this minute cheesy tubercle bacteria tuberculosis are distinctly seen in the remaining nuclei of tubercle cells, none of these organisms are met with entirely liberated from the nuclear protoplasm, either single, or forming larger groups, or aggregated in masses. On the contrary, after having reached a certain degree of development, they degenerate, die and disintegrate with the anatomical elements of the tubercle. As this condition of things is mostly found to exist in the smallest tubercles of typical cases of miliary tuberculosis, it explains the fact, observed and stated by some authors, that *not all tubercles contain bacteria tuberculosis*, and that, whenever they are met with, it is generally in the cheesy matter of old tubercles. I have microscopically examined the

lungs of a fair number of cases of miliary tuberculosis, without even being able to discover free and fully developed bacteria tuberculosis in the smaller or younger tubercles of these organs; whenever they were met with, it was always in the older and larger tubercles. In the miliary tubercles of the liver and spleen, on the contrary, I have not unfrequently encountered them liberated from the nuclei, and fully developed; in these cases, however, the lungs always contained small cavities, showing that the course of the disease was rather protracted.

In directing now our attention to figure 4 which represents a portion of a small miliary tubercle near its cheesy centre, magnified about 1,090 diameters, we observe the same condition as in fig. 3, with the exception that the anatomical elements, being more highly magnified, are more distinctly recognized. As in the preceding figure, we observe at *a* the bacteria tuberculosis developing in the nuclei of the tubercle cells; the outlines of these cells are not seen, on account of the object being mounted in Canada balsam and illuminated very highly with Abbé's illuminating apparatus. At *b* the same nuclei are seen, but out of focus, while *c* represents the inter-alveolar septa. Finally at *d*, a portion of the cheesy centre of the tubercle is represented, in which the disintegration of the nuclei and bacteria tuberculosis is distinctly seen.

The degeneration of the nuclei and imperfect development of bacteria tuberculosis is equally well exhibited in figure 10, representing some of the anatomical elements of a miliary tubercle of the liver, magnified 1,090 diameters. In this figure, we observe at *a* a group of normal hepatic cells from near the border of the tubercle; *b* represents a pair of hepatic cells from the periphery of the tubercle, the nuclei of which have

commenced to shrivel, while at *c* a number of nuclei from the cheesy centre of the tubercle are exhibited, the margins of which are shriveled in a higher degree and broken up into fragments. Some of these nuclei are still surrounded by the degenerating protoplasm of their cells. At *d*, finally, the ultimate minute fragments of the nuclei are represented, some of which have assumed the form of granular filaments.

In the cheesy centres of the older and larger tubercles, or tuberculous masses, met with in the lungs of cases of chronic tuberculosis, as well as in those of the larger tubercles found in the organs of protracted cases of miliary tuberculosis—especially when accompanied by the formation of small cavities in the lungs—the bacteria tuberculosis become fully developed and are liberated from the remaining protoplasm of the nuclei by its final complete degeneration. Although the gradual development of these bacteria, from their first appearance in the nuclei of the tubercle cells to their final liberation, and to their aggregation in larger groups, or masses, is not seen in the sections of every one of these tubercles, there are, nevertheless, many specimens met with—especially when looked for in the examination of very numerous sections—in which the whole process may be observed in one and the same section. It is from such a specimen that figure 5 was copied. This figure, also magnified 1,090 diameters, represents a small portion of a large tubercle from the lungs of a boy, sixteen years old, and affected with miliary tuberculosis of the lungs, liver, spleen, kidneys, and lymphatic glands; the lungs, from which the section was taken, contained several small cavities. The tubercle, though it had undergone the coagulation-necrosis, showed no cavity in the centre. In this figure, as in the preceding, *a* represents the bacteria tubercu-

losis developing in the nuclei of the tubercle cells, and *b* the same out of focus. At the upper portion of the figure, the borders of two neighboring alveoli are recognized, while *c* very likely represents some degenerated interstitial connective tissue, leading to the central part of the tubercle. In the latter we observe at *d* the bacterial groups commencing to enlarge in their dimensions, while at *e* we find them aggregated into small masses. In the sections, the latter present a purplish blue appearance, caused by those bacteria being buried deeper in the tissue, and in consequence out of focus.

Though I am as yet unable to assert anything positive as to the exact manner in which these aggregations of bacteria tuberculosis are formed, I think that it may take place as follows: When the bacteria contained in one nucleus have reached their full development, they may be liberated by the complete degeneration and disintegration of whatever has remained of the protoplasm of this nucleus, and then multiply in the protoplasm of the body of the cell, provided it has as yet not completely undergone the necrotic process. I doubt not but that in this manner the groups of bacteria, originally contained in the nuclei, frequently grow in dimension, and that this mode of growth has given rise to the idea, generally entertained, of these organisms being contained in the protoplasm of the tubercle cells. The groups, represented at *d* of figure 5, may have grown in this way. The larger aggregations of bacteria, represented at *e*, may have been formed in the same manner, that is, by a complete necrosis and fusion of the protoplasm of a number of neighboring cells, together with a numerical increase of the bacteria contained in these cells or their nuclei. The formation of these aggregations or masses of bacteria tuberculosis in the manner just indicated is very probable, for

the reason that by a close microscopical examination the original groups, forming these masses, may in many instances be still recognized.

In some of the miliary tubercles of the liver the development of the bacteria tuberculosis in the nuclei of the cells as well as their liberation from the latter and their aggregation into small masses is frequently well exhibited in one and the same section. In the preceding division of this treatise I have already mentioned that the secreting elements of the liver, the hepatic cells, appear to take a part in the formation of the tubercle; at any rate, bacteria tuberculosis are observed to develop in the nuclei of these cells. To illustrate this fact let us examine figure 8, which has been copied from a section of the liver of the boy of sixteen years, above mentioned, and represents a small portion of the parenchyma of this organ, bordering directly the periphery of the miliary tubercle, magnified about 625 diameters. In this figure we observe a number of hepatic cells (*a*) the nuclei of which still present a normal appearance, whilst in others the degenerative changes of these bodies, with the gradual development of the bacteria tuberculosis (*b*), are distinctly seen. In passing over the figure 9, representing a portion of the centre of the tubercle which has undergone the coagulation-necrosis—also magnified 625 diameters,—we observe a number of fissures (*a*) in the section which, very likely, represent the contracted lumen of the capillaries. At (*b*) the individual groups of bacteria tuberculosis, with the remains of the protoplasm of the nuclei in which they have been developed are distinctly seen. In passing from the upper to the lower part of the figure the bacteria of these groups are observed to increase in number until at (*c*) they appear as smaller or larger aggregations.

During the course of the development of the bacteria tuberculosis in the nuclei of the tubercle cells they appear both in the form of cocci or diplococci and of filaments composed of three, or even four cocci. The latter appear generally curved, and frequently lie parallel with the periphery of the nucleus, so that in the beginning of their formation they might be mistaken for the double contour of this body. That this is not the case, however, is easily discovered by observing the granular fragments into which the contour is broken up. The single granules, or cocci, do not represent the normal granules contained in the nuclei, as might be thought; this is proved by their retaining the purple color of the magenta when subjected to the action of decolorizing agents, a property which the latter do not possess. Besides the normal granules of the nuclei occupy the interior and not the periphery of these bodies. But, as not all the nuclei of the tubercle cells contain bacteria, the difference between these organisms and the normal organic granules is easily recognized by the latter being stained, like their nuclei, with the second color of the section.

In sections made of tuberculous lung tissue bordering a smaller or larger cavity, the gradual development of the bacteria tuberculosis may also be frequently observed. In the tuberculous tissue, forming the walls of the cavities, which is generally more or less indurated, the bacteria may still be contained in the remains of the protoplasm of the nuclei, whilst at the very borders of the cavity, as well as in the layer of inspissated purulent matter, by which the latter is generally lined, groups of free bacteria may be met with. By the breaking down of the tuberculous tissue the bacteria get into the purulent matter contained in the cavity, and with this into the expectorations of the patient. Not in every instance, however,

are bacteria tuberculosis met with in the sections taken from the borders of pulmonary cavities, a circumstance which explains the fact of the occasional absence of these organisms from the expectorations of tuberculous patients.

The development of bacteria in the protoplasm of the nuclei of irritated and degenerating cells, however, is not only observed in tissues affected by tuberculosis, but also, as I shall show directly, in the neoplastic degenerating cells of organs affected by other diseases, such as leprosy, carcinoma, etc.

In the same manner as tuberculosis is characterized by the presence of the bacterium tuberculosis in the tubercles of the organs affected by this disease, leprosy is characterized by the so-called *Bacillus leprae*. This organism, though called a bacillus, presents itself still more distinctly in the form of very minute cocci than the bacterium tuberculosis. The chief difference found between the two organisms consists in the cocci of the bacterium of leprosy being smaller than those of the bacterium tuberculosis, as well as in the filaments formed by these cocci being almost always straight. With the view of closely investigating the morphological characters of the bacillus leprae, I amputated in the summer of 1883 the lobuli of the ears of two living leprous patients. The examinations made on the material thus obtained were not only confined to thin sections, but extended to the fresh blood oozing from the cut vessels, and to the matter scraped with a sharp knife from the freshly cut surface of the lobules. All the preparations were carefully stained by Gibbes' method with magenta and chrysoidine. In the matter scraped from the cut surface of the lobuli I met, as I had expected, with single leprous cells, detached from the connective tissue of the skin by the scraping process, which contained single cocci, diplococci, and filaments

composed of three or four cocci, representing the bacillus leprae.

In the stained preparations which I had carefully made of the blood oozing from the cut vessels of these lobuli, I discovered the same organisms, showing the morphological characters, above mentioned, still more distinctly than in the leprous cells. They were here observed attached in the form of groups to the colorless blood corpuscles, the number of which appeared to be abnormally increased. The protoplasm of most of these corpuscles had undergone degeneration and disintegration, the bacteria appearing liberated, or adhering to the remains of the likewise degenerated nuclei (fig. 12, magnified about 1090 diameters). Subsequently to this observation a number of other preparations were made of leprous blood, taken from different parts of the skin of three leprous patients by my young friend Dr. E. Laplace, at present sojourning in Paris, who was, at that time, the student assistant of the Pathological Department of the Charity Hospital. In all these preparations the same organisms were found, exhibiting the characters above described. Although a number of opportunities were offered to me, since that time, to examine the blood of other lepers, I neglected to do so for the want of time; until during the summer of 1885, when I again examined the blood taken from the arms of two other leprous patients, without meeting, however, with any bacteria contained in this fluid.

The same form of bacteria as those met with in the blood were observed in the protoplasm of the cells and their nuclei in the pus covering the healing surface of the ears, from which the lobuli had been cut. In the matter taken from a pustule of the skin of another leprous patient, a woman, the bacteria

were met with mostly in the form of granular filaments in the nuclei of the leucocytes.

In the sections, made from the amputated lobules of the ears, I found, likewise, the bacteria developing in the nuclei of the neoplastic cells. But, as many of the cells contained in such a section had undergone fatty degeneration, and, in consequence, were filled with a number of smaller or larger fat globules, whilst at the same time they contained quite a number of nuclei, formed from the original nucleus by the process of division—and which eventually undergo degeneration—a careful examination is required to clearly understand the exact location of the bacteria in the larger kind of these neoplastic cells. For this reason our attention should be directed to those cells, of which the protoplasm has as yet not undergone fatty degeneration, and in which the multiplication of the nuclei has not advanced too far. In these cells the bacteria will be seen developing in the nuclei (fig. 14, *a*, *b*, and *c*); and, when closely examined with a good homogeneous immersion objective of a sufficient magnifying power, and illuminated with very oblique light, they will show that they are composed of minute cocci, appearing in bas-relief-like minute beads, and exhibiting the character of a true *sphero*-bacterium. In consideration of this fact I do not hesitate to call hereafter the so-called *Bacillus leprae* by its proper name, the *bacterium leprae*.

In the latter part of the spring of 1884, another fair opportunity of investigating the morphological characters of the *bacterium leprae* was offered to me by the death of a severe case of leprosy at the Charity Hospital. The microscopical examination of the tissues of the lungs, liver, spleen, kidneys, epiglottis, etc., fully corroborated the correctness of my pre-

vious observations concerning the bacterium leprae. In the liver and spleen the development of these bacteria in the nuclei of the cells was particularly well exhibited, as will be seen by referring to figure 11. In this figure, which represents a small part of a thin section of the liver, stained by Gibbes' method, and magnified about 625 diameters, we observe at *a* the normal nucleus of a hepatic cell, while that of a neighboring cell, at *b*, shows the beginning of the degenerative process by the shriveling of its margins. In proceeding to *c*, we find the outlines of the nucleus obliterated and the bacteria leprae nearly developed; while finally at *d* they are seen completely liberated from the degenerated protoplasm of the nucleus and disseminated through the likewise degenerating protoplasm of the body of the cell.

Finally in the summer of 1885 I took occasion to convince myself once more of the correctness of my previous observations, by examining very thin sections made of a leprous tubercle cut from the arm of a living patient, and also stained by Gibbes' method. Small portions of one of these sections I have represented in figures 13, 14 and 15. The first of these (fig. 13) represents a minute portion of the pars reticularis of the corium of the skin from the very margin of the tubercle, where the pathological changes of the connective tissue cells are still in the incipient stage of the disease; it is magnified 625 diameters. In it, we observe a considerable number of the nuclei of these cells (*a*) distributed throughout the fragments of tissue containing bacteria leprae in their early stage of development. Of these cells, only a small number (*b*) are seen in an advanced stage of fatty degeneration with the fully developed bacteria leprae between the fat globules. In figure 14, which represents a minute part from the middle of the tubercle, and also

magnified about 625 diameters, the bacteria are seen in the different stages of their development. Thus at *a* their first appearance is noticed in the nuclei of the unchanged connective tissue cells, whilst at *b* they are slightly more developed. At *c* the nucleus has disappeared by degeneration, and the bacteria are seen fully developed in the protoplasm of the cell, exhibiting very distinctly their grander character. Finally at *d* they are, as before, met with fully developed between the flat globules of the degenerated cells. In figure 15, which represents a number of degenerated leprous cells, magnified about 1090 diameters, the morphological character of the bacteria leprae is still better recognized than in the preceding figures.

In order to ascertain whether, like in the nuclei of the cells of tuberculous and leprous tissues, bacteria would also develop in those of other morbid growths, I examined during the course of the above described investigation, the sections of quite a number of fresh tumors, or other neoplasms, stained by Gibbes' method. Although in the greater number of these specimens bacteria were not met with, I nevertheless found my suspicions verified in distinctly observing in four instances the development of these organisms in the nuclei of the neoplastic cells in the same manner as I have described it above. The first of these instances relates to a small lobulated tumor, about $\frac{5}{8}$ inch in diameter, a so-called polypus of the mucous membrane of the rectum, removed from very near the verge of the anus. In examining the sections of this tumor, I met in some places of the hyperplastic connective tissue a large number of cells the nuclei of which contained granular bodies resembling bacteria. That these bodies in reality represented bacteria, was proved

by their being intensely stained purple, or purplish blue, by the magenta, while the protoplasm of the nuclei was stained yellow by the Bismarck brown. They presented themselves mostly in the form of cocci, or diplococci, but there were also some filaments observed, composed of three cocci. The diameter of these organisms was about the same as that of the bacteria tuberculosis, though among them a number of single cocci of a still larger diameter were noticed. In the nuclei of a small number of the deeper cells of the epithelium covering this tumor, as well in some of the Lieberkuehn's glands, the same bacteria were met with. Although the sections of this tumor were made, stained and mounted in Canada-balsam in January, 1884, the bacteria were seen as distinctly as ever when re-examined in September, 1885, though the purplish blue of the magenta had faded into a dark red. The next specimen, in which I met with bacteria in the nuclei of the cells, was a carcinoma of the mammary gland. There they also appeared in the form of cocci and diplococci, but, as in the preceding case, only in certain places of the section. In both instances the bacteria were strictly confined to the protoplasm of the nuclei.

In the third specimen, however, representing a carcinoma of the stomach, the bacteria were observed to develop in the same manner as those in the nuclei of the cells of tuberculous or leprous tissues, that is, commencing with the shriveling of the nucleus, and the breaking up of the margin of this body into minute fragments, and terminating in the formation and liberation of granular filaments. In this case also, the bacteria were only met with in

certain localities of the section, especially in the cells of the fibrous coat of the organ. In the fourth morbid growth, representing a so-called endothelial cancer, the whole process of development could also be traced from the shriveling of the nucleus to the ultimate formation and liberation of the bacteria, which, in some places, were met with aggregated in the form of small groups. Some of these groups were formed by three or four filaments lying at certain angles toward one another; sometimes in the form of a circuit, resembling a ring broken into fragments, and corresponding in size to the nuclei in which they had developed. Most of the filaments were more or less bent or curved.

The bacteria met with in these two last neoplasms did not exhibit the deep purplish-blue, observed on the fully developed bacteria tuberculosis and leprae when stained with magenta, but rather a purplish red. This want of deepness in the stain was undoubtedly owing to their not having as yet reached their highest development. This same phenomenon is frequently observed during the development of the bacterium tuberculosis in the nuclei of the tubercle cells, as I have once mentioned before.

The results of my examinations of these four neoplasms then show, that the development of bacteria in the nuclei of certain cells does not exclusively take place in tuberculous and leprous tissues, but also in other morbid growths, whenever the special conditions required for their evolution are present. What these conditions are, would be difficult to determine at our present state of knowledge, though it is not improbable that they may be found in a certain form of degeneration of the elements of these tissues, such as the

coagulation-necrosis, which cannot be said to be confined to the tubercle of tuberculosis. The tumors, of which I stained sections for the purpose of discovering bacteria, though representing a fair number, are far from comprising all those which I examined during the course of these investigations, as, otherwise, the number of specimens in which bacteria were met with might, perhaps, have been larger. But as the time which I could spare for the search of bacteria in other than tuberculous and leprous tissues was rather limited, I confined my examinations only to specimens which presented certain phenomena of involution or decay, and contented myself with the four instances above mentioned.

VI.

BACILLUS TUBERCULOSIS. CONCLUSIONS FROM THE RESULTS OF
INVESTIGATION.

In reviewing the results of my investigations into the nature of the bacterium tuberculosis and its relation to the human lungs, or other organs, it will be found that, excepting the development of this organism in the nuclei of the tubercle-cells, they correspond, perhaps, in most other points to the statements previously made by other authors. The development of the bacterium tuberculosis in, or, as it almost appears, from the protoplasm of these nuclei is a phenomenon, not only difficult to explain, but which, moreover, may yet bear importantly upon the whole bacterium tuberculosis question. Hence it is worthy to be presented to the reader in its proper light, which, however, involves a review of other obscure points in the history of the bacterium tuberculosis, especially of the manner in which this organism is said to gain access to the human lungs, or other organs.

When Koch, in 1882, announced his discovery of the bacillus tuberculosis, he asserted it to represent the original and special cause of tuberculosis, demonstrating, at the same time, the manner in which it had gained access to the human lungs as to give rise to the tubercle of tuberculosis. His explanation was mainly based upon the supposition, that these special bacteria were constantly floating in the air; and that, accordingly, some, or even one, of them would enter the human lungs during the act of inspiration; and, being carried by the inspiratory current of air to the terminations of the bronchial system, the air-vesicles, settle there upon one or the other epithelial cell, lining these minute cavities; the irritation, set up in the protoplasm of this cell by the presence of the parasite, was to be regarded as the first impulse given to the formation of the tubercle.

It is, particularly, the giant-cells of the tubercle which Koch regards as the special seat of the infectious agent; *for he says, as soon as they make their appearance in the tubercles, bacilli tuberculosis will be regularly met with; if the number of the latter in the tubercle is very limited, they will almost always be found in the giant-cells; and, then, never more than one, or a few individuals in each cell. But when, in correspondence to a more intense course of the process, the bacilli are present in large numbers, then many, fifty or more, will be found enclosed in one giant-cell. The arrangement of these organisms in the giant-cells, Koch states, often takes place in a peculiar manner, namely: If there is only one bacillus enclosed in a cell, it will mostly be found in the centre of the latter, or very little excentrically; but, if the nuclei are lying closely together near, or at one end or pole of the cell, then the bacillus will be found at

* "Die Aetiologie der Tuberculose," von Dr. R. Koch, reviewed by Litten. "Deutsche Medicinal Zeitung," March 24, 1884.

the other end, that is, in that part of the cell which is free from nuclei. This arrangement of the nuclei opposite to the bacillus, Koch regards as a manifestation of an "antagonism," existing between the nuclei of the giant-cell and the parasite therein enclosed, causing the former to get as far as possible away from the latter; even if the bacilli in the giant-cell increase in number, this "oppositional" grouping of the nuclei may still take place, though then, an entirely different arrangement of the bacilli is generally observed. To Koch it almost appears that with the numerical increase of the bacilli, their attitude (*Haltung*) or bearing toward the nuclei becomes more active; for, he says, they then advance more and more toward the periphery of the cells; and, inserting themselves between the nuclei, finally even break through the walls of these bodies. Besides, the destruction of the giant-cell appears to follow regularly such an increase of the bacilli: for very often, in the vicinity of giant-cells containing bacilli arranged in a radiating manner, and in a direction toward the interior of the tuberculous centre, groups of bacilli are met with, which, though not any more enclosed in brown-colored nuclei, still show the same radiating arrangement. As many transitive forms are besides met with, it cannot be doubted that such radiating groups of bacilli indicate the places of former giant-cells, of which the nuclei have disappeared, and of the contents of which only the bacilli have been left.

The above mentioned statements of Koch show that he attaches much importance to the relationship existing between the bacteria tuberculosis and the giant cells. As far as I am able to interpret these statements, he regards the appearance of these giant-cells and that of the tubercle-bacteria as occurring almost simultaneously, though it is not stated whether the bacterium gave rise to the giant-cell, or whether the latter pro-

duced the former. If the number of bacteria is very limited, Koch finds them always confined to the giant-cells, but never more than one, or a few individuals in each cell. From this I cannot but infer, that he regards these individuals as the original bacteria, carried by the inspiratory current of air to the interior of the air-vesicles of the lung, where, by irritating the protoplasm of one or the other lining epithelial cells, they give rise to the formation of a giant-cell. Although the exact nature of these giant-cells is as yet not positively known, we shall in this instance, nevertheless, suppose that they represent irritated epithelial cells, the nuclei of which have multiplied by division, while the protoplasm of the cells has simply increased in bulk without division. The inference to be drawn from Koch's observations on the giant-cells would be as follows: The bacterium, after having caused by its presence the multiplication of the original nucleus and the increase of the protoplasm of the cell, quietly remains in one corner of the latter, while the nuclei, being, as it appears, afraid of the parasite, get away as far as possible from their antagonist by withdrawing to the other corner. But, now, the bacterium also commences to increase in number by reproducing its own kind, and, as soon as its descendants are sufficiently numerous, their attitude toward the nuclei becomes more active; for, advancing like so many soldiers, toward the periphery of the cell, they commence the attack upon the nuclei by inserting themselves between these bodies, and finally conquer by breaking through their walls and by settling in their interior. Thus the "antagonism," which Koch supposes to exist between the bacteria and the nuclei of the giant-cell, leads to the destruction of the latter, and to the remaining of the former upon the field of battle.

As far as my own observations extend I may state that I

have never observed the above described phenomenon concerning the bacteria tuberculosis and the nuclei of the giant-cells, which, if true, would almost indicate that these bodies were endowed with a certain kind of instinct, manifesting itself in the "antagonism" to which Koch directs attention. On the contrary, I have met with many giant-cells containing no bacteria tuberculosis, whilst in others I found a smaller or greater number of these organisms enclosed, both in the nuclei and in the protoplasm of the cells. In the same way giant-cells are met with containing a considerable number of nuclei, arranged in line along a part of the periphery of the cell, whilst in others again they are, in smaller or larger numbers, irregularly distributed throughout the protoplasm of the cell. On the whole, I can find no reason for supposing a closer relationship to exist between the giant-cells and the bacteria tuberculosis than between the latter and the other cells of the tubercle. In those instances in which I met with bacteria tuberculosis in the giant-cells I found them either still enclosed in the nuclei or liberated from the latter by the ultimate disintegration of their protoplasm, lying free in the degenerated protoplasm of the cell. But let us now endeavor to find some plausible explanation for the presence of the bacteria tuberculosis in the nuclei of the tubercle cells, in which, as I have shown before, they make their first appearance, and to which they may gain access by different means and ways. Before, however, entering upon this discussion I shall take the liberty of quoting from Litten's review, already mentioned, Koch's views on the subject. They are as follows: "The appearance of one or some bacilli in the interior of cells, bearing an epithelioid character, must be regarded as the first stage of the origin of the tubercle. The manner in which the bacilli get into these cells can hardly be explained in any

other way but that, not being themselves endowed with spontaneous motion, they are either in the current of the blood or lymph or in the tissues of already existing tuberculous centres, taken up and carried along by tissue-elements which possess this kind of motion, as, for instance, the wandering cells. The peculiar fact that single bacilli, or small groups of them, separated from each other by one and the same, though comparatively far, distance, are frequently met with, can only be explained in this manner. Charged with such parasites, the cell is still capable of traveling considerable distances, but under the deleterious influence of the bacillus it undergoes changes which will soon cause it to stop. Whether, now, one wandering cell is destroyed and the bacilli are taken up by other cells present at the same place, and which subsequently assume an epithelioid character,—or whether, what Koch thinks to be more probable, the wandering cell, transporting the bacillus is transformed into an epithelioid cell and from this into a giant-cell must, for the present, remain undecided. In order to presume that the bacilli are originally carried along by the wandering cells and that in this manner their distribution in the tissues is effected, the following reasons may be adduced. First, the analogy with the septicæmia of the mice, in which also rod-shaped bacilli are incorporated by colorless blood-corpuscles; furthermore, the direct observation, showing that the tubercle bacilli are first taken up and transported by the wandering cells. This is best recognized in those cases in which large numbers of bacilli are introduced into the circulation, as, for instance, by injection into the veins of the ear of the rabbit. If an animal, infected in this manner, is killed at an early time, numerous leucocytes enclosing one or some bacilli are then still found in the blood; whilst even in the tissues of the lung, liver and spleen true round cells now and

then appear which, containing a single or divided nucleus, show as yet no epithelial form; that is to say, they resemble in every respect colorless blood-corpuscles, though containing tubercle bacilli. The same phenomena were observed in guinea-pigs, into the abdominal cavity of which large numbers of tubercle bacilli were injected, and which died already during the course of the first week. A third reason for the above mentioned supposition may be found in completely dead tissues, that is, in such places where the influence of living cells upon the bacilli is entirely excluded; for if here a vigorous growth of bacilli once more occurs, they will arrange themselves in entirely typically formed groups resembling the peculiar forms of bacteria-colonies in the pure culture upon the serum of blood. These forms have to be regarded as those assumed by the tubercle bacilli when developing without disturbance, and when their grouping is solely determined by those local changes of position which depend upon their growth. Every other arrangement must be regarded as caused by some other disturbance. If a too rapid increase of the bacilli within the giant-cells takes place, the latter undergo destruction in being to a certain extent burst by the bacilli pressing themselves between the walls of the nuclei. The nuclei disintegrate into minute granules, and the cell is destroyed. The further changes, taking place in the tuberculous tissues after the development of the epithelioid and the giant cells, are all of a retrograde nature. The greater part of them belongs to those processes known as coagulation-necrosis, and lead to the death of the tuberculous tissues, and to the formation of the so-called cheesy masses which are so frequently found in tuberculous centres. Generally the tubercle-bacilli disappear very soon in the cheesy masses, so that they are only met with in the younger centres (Herden), while they are almost always absent

in the older ones. In other cases, however, a simple shriveling and transformation of the tuberculous tissue into a firm connective tissue may take place after the disappearance of the bacillus-vegetation.”*

Now let us briefly review the above quotation from which we gather that the appearance of one, or some bacteria tuberculosis in the interior of cells bearing an epithelioid character, is regarded by Koch “as the first stage of the origin of the tubercle,” and that, furthermore, the manner in which the bacteria get into these cells can hardly be explained in any other way but that they themselves, being incapable of moving, must be taken up—either in the current of blood or lymph, or in the tissues of already existing tuberculous centres—and carried along by other tissue elements which possess spontaneous motion, such as the wandering cells. The conjecture concerning the transportation of the bacteria tuberculosis by means of wandering cells, appears to me very plausible, especially since I have observed the same phenomenon in the blood of lepers, where I found the bacteria lepræ adhering to the remains of colorless blood corpuscles. But with this conjecture the presence of these organisms in the tubercles of tuberculosis, and particularly in the nuclei of the tubercle cells, is as yet not explained, even not in accepting the theory of the tubercle being originally formed from wandering cells, derived from the blood or lymph, for it is obvious that the bacteria, in order to be taken up by these cells, must already be present either in these fluids, or in already existing tubercles. But as to the particular manner in which the bacteria first gain access to these fluids, or to the parenchyma of the lungs, nothing is said in this place; and, as no other satisfactory explanation on this point can be found in Litten’s review

* Page 261.

of Koch's paper, I propose to discuss the different ways and manners in which the bacteria might possibly get into the tissues of the human lungs, or other organs.

The bacteria tuberculosis, being incapable of moving spontaneously, must of course be transported from one place to another by some other agent or moving power. If, therefore, they are, as Koch asserts, constantly present in the air we breathe, it is but natural to suppose that one, or some of them might be carried, as once before mentioned, with the inspiratory current of air into the interior of the alveolar cavities of the lungs, and settle there upon some of the lining epithelial cells. Having settled upon one of these cells, however, the bacterium being motionless, is incapable of penetrating through the protoplasm of the cell into the nucleus, except by decomposing and absorbing the protoplasm before it. This phenomenon is observed among some of the more highly organized fungi, as, for instance, with the so-called potato-fungus (*Peronospora infestans*), which, though being, like the bacterium tuberculosis, incapable of moving spontaneously, nevertheless penetrates not only into the cells of the potato, but, moreover, even into the starch-granules contained therein. The penetration in this case, however, is solely effected by the inherent growth of the fungus, that is, by the lengthening of its filaments, which, in channeling their way into the interior of the cell, absorb a part of its wall. Thus, the further the fungus penetrates, the more its filaments gain in length.

Although it is not very probable, I will, for the sake of argument, suppose that the bacterium tuberculosis, after having settled upon the epithelial cell penetrates in the above-mentioned manner into the interior of the nucleus, whilst it, at the same time, increases in numbers; in this way it might even penetrate from cell to cell. But instead of proceeding with

our supposition, let us now direct our attention to the tubercle, which, according to Koch, has to originate in the epithelial cell, irritated and already partly destroyed by the bacteria. The tubercle, as we know, can only be formed by the multiplication of one or more cells, brought about by the successive division of the nucleus and the protoplasm of the original cell. The question, therefore, arises: Is a cell, which is already partly destroyed by bacteria, still capable of multiplying; or does it still possess sufficient vitality to give rise to the hundreds or thousands of cells of which a tubercle is formed? For my own part, I cannot but answer the question in the negative. But in admitting even the possibility of the tubercle arising from an epithelial cell, already crippled by bacteria, there are besides other phenomena remaining to be satisfactorily explained. One of these is the simultaneous origin of great numbers of tubercles throughout one, or even both lungs, as is frequently witnessed in acute miliary tuberculosis. In such a case, it is quite difficult to suppose that so many bacteria, as there are tubercles, had simultaneously entered the lungs, and that—while passing through the numerous bronchi and bronchioles—they should distribute themselves so nicely as to settle only in the interior of certain alveoli throughout the whole organ, separated from one another by certain, though frequently quite small, distances, as found between the respective tubercles supposed to be called forth by these bacteria. The appearance of tubercles, separated from one another by greater or lesser distances, has been explained by supposing that the bacteria are transported from one part of the lung to the other by means of the expectoration; that is to say, by the matter derived from a small cavity, and charged with bacteria, passing outward through one of the smaller bronchial tubes into the larger parent tube, and then returning through another

branch of the latter to the terminal lobules of another part of the organ. In answer to this supposition we may say, that it is possible but not very probable, as the normal direction of the secretion is from the smaller bronchi toward the larger ones, the same as that of the movements of the cilia of the epithelial cells lining the bronchi, and assisting in the forward movement of the secretion. But the main objection to this supposition will be found in the fact that not unfrequently cases of miliary tuberculosis are met with in which no cavity whatever can be discovered, though innumerable tubercles are disseminated throughout the whole organ.

There is another mode of explaining the transportation of bacteria from one tubercle to a distant part of the lung; it is the same as that used to explain the phenomenon of metastasis observed in certain morbid growths, that is, through the lymphatics. The fact that all tissues contain lymphatic channels or vessels, makes it appear very plausible that certain neoplastic cells might, in one way or the other, get into these channels to be carried by the lymph-current to other parts of the same, or even of another organ. Such an occurrence, it is true, may happen, but not as easily as is generally supposed.

The lymphatics commence, as we know, in the so-called lymph-spaces, representing minute, irregularly-shaped channels extending, especially through the connective tissues, where they are identical with the interspaces of the fibrillar bundles of this tissue and lined, though incompletely, by endothelial cells. In these channels the radicals of the lymphatic vessels commence. Each organ generally possesses a deep and a superficial set of lymphatic vessels. The radicals of the deep lymphatics, after having arisen from the lymph-channels, generally follow the minute bloodvessels, and, soon joining one another, form larger lymphatic vessels. By successively continued junctures of the

latter, the larger lymphatic vessels are formed, which, also following the bloodvessels, finally leave the organ to join the nearest lymphatic glands. But while the radicals of the deep lymphatics, after arising from the lymph-spaces, soon join one another, to give rise to larger lymphatic vessels, those of the superficial lymphatics first form a network which extends over the surface of the organ, and from which the lymphatic vessels subsequently arise. The lymphatic vessels, leaving the lymphatic glands, form larger vessels which finally join one or the other lymphatic duct. Some communications always exist between the deep and the superficial lymphatic vessels of an organ. All lymphatic vessels are provided with valves, which open in the direction of the lymph current, that is, toward the opening of the lymphatic ducts into the subclavian veins, or, in other words, toward the heart. Even the radicals of the lymphatic vessels possess these valves, the presence of which is indicated by a constriction in the wall of the vessel. Many years ago, I injected the lymphatics of the human liver with Prussian blue and even observed these constrictions on lymphatic vessels, smaller in diameter than the capillaries of the blood. From this we may presume, that the current of lymph can only run in one direction. In the lymphatic network on the surface of an organ the current may run sideways or backward into neighboring radicals, but only to a very small extent, as even here, its general direction is toward the lymphatic vessels arising from this network. The lymph-current, joining the blood-current in the subclavian veins, runs of course in the same direction with this, and is, therefore, controlled and kept in motion by the same power, upon which the circulation of the blood depends, that is, the suction-power of the heart. Hence we may presume that the lymph-current, from its very beginning in the lymph-spaces, cannot deviate from its

course, but is bound to take the most direct course toward the heart. For this reason we are justified to presume that, if ever bacteria tuberculosis are taken up by the radicals of the lymphatics of the lung, they will be carried by the lymph-current directly to the heart, and not to a distant terminal lobule of this organ, except through the medium of the circulation of the blood. Having once entered the blood, the bacteria might attach themselves to some of the colorless blood-corpuscles, and pass with these through the walls of the capillaries of one or the other organ, and thus give rise to the formation of new tubercles.

The formation of tubercles in this manner is not impossible, though quite improbable; for if this were the case, bacteria tuberculosis would much more frequently be met with in the blood of tuberculous patients than they have in reality been met with thus far. To the extent of my knowledge, there are only three authenticated cases, reported by Weichselbaum, in which these bacteria were found in the blood after death. In these cases cheesy tubercles were found in the uterine veins and Fallopian tubes, in the pulmonary artery, and around the pudendo-vesical plexus, where they had perforated a vein. In ten other cases Weigert has observed tubercles in the veins, and in two others tubercles in the thoracic duct; while tubercles in the latter locality had been previously observed in one case by Ponfick. In the reports of Weigert's and Ponfick's cases, however, nothing is said of the presence of bacteria tuberculosis in the blood, though, if they had really been present in this fluid, it would be obvious that they had entered it directly with the cheesy matter of the tubercles, and not by way of the lymphatics. Nor can the presence of tubercles in the walls of the veins be regarded as an unusual phenomenon, for they are equally met with in the walls of other vessels, or

in the peritoneum and other fibrous structures. I have myself stained the blood of several tuberculous patients by Ehrlich's and Gibbes' methods, but failed to discover any bacteria tuberculosis.

From what I have said above it will be seen, that the theory of the formation of tubercles in the human lungs from one, or several of the lining epithelial cells of the alveoli, previously irritated and crippled by bacteria tuberculosis, is rather resting upon a weak foundation, for if the tubercle was really originating in one or more of these cells, its formation could only be effected by a successive division and multiplication of the latter. In admitting, however, the possibility of the formation of the tubercle in this manner, we must likewise admit that a cell, the nucleus of which is undergoing a process of involution by the presence of bacteria in its protoplasm, is still capable of reproducing its kind. In this case the bacteria would be transmitted from cell to cell by the division of the mother-cells. But, even if this theory regarding the origin of the first tubercle were true, it would still fail to explain the simultaneous arising of hundreds, nay, in many cases, thousands of other tubercles, separated one from another by healthy parenchyma in the same lungs.

In the preceding section of this treatise I have shown that the bacteria tuberculosis first appear in the nuclei of the tubercle cells. Simultaneously, or even previously to the appearance of the bacteria in the nuclei, not only a gradual shriveling in the protoplasm of these bodies, but, in many instances, also a breaking up into several fragments is observed, the whole phenomenon indicating the going on of a process of involution. The same phenomenon is also observed, as I have already stated, in the nuclei of the cells of cancerous, or other neoplastic growth, while they are undergoing a certain kind of

degeneration; and, furthermore, in the nuclei of pus-cells and other leucocytes, as, for instance, the exudation cells of croupous pneumonia, or even in the nuclei of the epithelial cells of the bronchioles, met with in phthisical and pneumonic expectorations. In the nuclei of the tubercle cells this process of involution, manifesting itself by the shriveling and breaking up of the protoplasm of these bodies, is accompanied, as I have shown, by the appearance and development of bacteria tuberculosis.

Now the question may be asked: How is it possible for the tubercle to develop, if a tubercle-cell is rendered incapable of multiplying itself, as soon as bacteria appear within its nucleus? This apparent contradiction is easily explained in considering that the bacteria tuberculosis, even in incipient tubercles, do not appear in the nuclei of the younger tubercle-cells, but rather in those of the cells first formed. Besides, it is not in the nuclei of all the cells of a tubercle that bacteria will be met with; on the contrary, in every tubercle a considerable number of cells is observed, in which the nuclei present their normal form, and where no bacteria can be demonstrated, even after the most careful staining. I have already stated that the nearer the cells of a tubercle are to its cheesy centre, representing the part of the tubercle first formed, the more highly developed are the bacteria, and *vice versa*; though I must say that, now and then, I have observed bacteria in some of the nuclei of the lining cells of alveoli, adjacent to a tubercle, and apparently free from tuberculous growth. These cases, however, are exceptions to the rule. From these observations we may justly presume, that not all cells of the tubercle are in one and the same condition, but that, on the contrary, one part of them may be normal, while the rest is undergoing a process of involution or degeneration; it is in the nuclei of the latter that

the bacteria tuberculosis find the proper soil for their development.

In the preceding pages I have discussed some of the ways and manners in which the bacteria tuberculosis might gain access to the nuclei of the tubercle-cells, while showing at the same time the objections which render these suppositions implausible. But having thus far failed to offer an explanation more satisfactory than those already discussed, the reader would now be justified to ask for the *true* manner in which these bacteria originally get into the interior of these nuclei, where, according to my observations, they are developed. Often, during the course of my investigations, I have put this question to myself, but I must confess that hitherto I have completely failed to answer it satisfactorily, because every attempt to solve this problem leads the inquirer unconsciously to one or the other field of speculation. But, being more accustomed to deal with facts than with theories, or hypotheses, I shall further remain content with my ignorance on this part of the subject, until the facts, which I have observed, will be corroborated and properly explained by other investigators. This, however, will not prevent me from simply pointing out the manner in which alone the origin and development of bacteria in the nuclei of neoplastic cells could be *hypothetically* explained. This is as follows:

The observation of the bacteria appearing in the nuclei, before they are seen in the protoplasm of the cells, without being able to explain, on account of their incapacity of moving spontaneously, the exact manner in which they gained access to these bodies, naturally leads to the suggestion that they must have originated there. The observed fact, however, that these organisms are not present in the nuclei of all the cells of a tubercle, or of any other neoplasm, suggests furthermore, that

the condition of the protoplasm of the nuclei containing bacteria, must be different from that of those nuclei containing none; that this is really the case is proved by the difference observed in the morphological appearance of these nuclei, as I have sufficiently demonstrated before. Now, there are two hypotheses which might explain the origin of the bacteria in the substance of the nuclei. The one consists in supposing that certain germs, too minute to be detected by the microscope, are constantly present in the nuclei of the cells of the organism, to which they were carried by the nutritive fluid of the latter, the liquor sanguinis, and incorporated with the normal substances of nutrition contained in the fluid. These germs, then, remaining dormant during the normal condition of the cells and their nuclei, might be developed into bacteria as soon as degeneration of the latter takes place.

The second hypothesis is identical with H. CHARLTON BASTIAN'S theory of *heterogenesis*, according to which low organisms, such as bacteria, may be directly formed from the protoplasm of animal cells, the vital activity of which is on the wane, or, in other words, undergoing involution, as, for instance, is witnessed in the tubercle of tuberculosis. When Bastian advanced this theory, a number of years ago, it met, like his theory of "spontaneous generation," with a great opposition, because it did not correspond with the predominating idea, that such organisms must be the offspring of a parent of their own kind. For my own part I cannot blindly discard the theory of heterogenesis, for the reason, that it does not appear to me entirely impossible, that the normal arrangement of the molecules of the protoplasm of the nucleus of an animal cell might under certain conditions of the organism be altered in such a manner as to correspond with that of the molecules of vegetable protoplasm; nor is it proved that such a molecular

change in the protoplasm of an animal cell is altogether impossible. On the contrary, it will appear more probable in considering that a difference already exists in the molecular composition of the protoplasm of the nucleus and that of the body of the cell, manifesting itself by the difference in the reactions of certain agents on these protoplasts, as, for instance, acetic acid dissolving the protoplasm of the body of the cell, while it leaves the nucleus unaffected. Furthermore, in staining animal tissues containing bacteria, as sections of tubercle, with aniline colors by Ehrlich's method, this dissimilarity in the molecular composition of the protoplasm of the nuclei and that of the bodies of the cells is rendered very striking by the fact that, while the latter offers no resistance whatever to the decolorizing action of the acids, but readily parts with the color previously absorbed, the former resists to a certain degree, retaining mostly some of the color, though not as much as the bacteria. The resistance of these nuclei to the decolorizing action of the acids even increases, whenever their normal condition is altered. The phenomena just described certainly indicate a similarity of molecular composition existing in the protoplasm of the nuclei of animal cells and in that of the lowest vegetable organisms, such as the bacteria. And in considering this fact a little more closely, the idea,—that under certain conditions of the cell and its nucleus a certain process of involution is set up, by which the constituent particles of the nucleus might, according to Bastian, "individualize themselves" and grow into lower organisms,—will appear less absurd than it has hitherto been regarded. Besides, if it is possible, as we must presume, that at one time or another in the early history of our globe, higher organisms developed from lower ones, while the latter originally arose from a primitive formless protoplasm, then it may not be impossible that

the lowest organisms in nature, represented by the bacteria, might spontaneously arise from the still living protoplasm of the nucleus of an animal cell, which under certain unknown conditions had assumed the nature of vegetable protoplasm. Such a process, if even not probable, is at least possible. In the consideration of a question, like the one before us, however, we should always remember that, though modern science has deeply penetrated into the secrets of nature, many natural processes are still left hidden to us. To these belong the mutual relations of the molecules of animal and vegetable tissues, of which our knowledge is rather deficient, for the reason, that molecules cannot be seen, though it is essential that, in order to render the explanation of those phenomena generally manifested by matter more easy, they should hypothetically exist in our mind. The same is the case with Bastian's theory of "heterogenesis" which, at least in some instances, would satisfactorily explain, as I shall demonstrate directly, the action of certain specific and contagious poisons. To demonstrate this, however, a few remarks on the most important property of the bacterium tuberculosis, namely, that of giving rise to the tubercles of tuberculosis, will be necessary.

Although the question whether the bacterium tuberculosis is in reality the direct inciting cause of tuberculosis in man, is not definitely settled, Koch's discovery of tubercles being artificially produced in the lungs, or other organs of certain animals, by the introduction of this organism into the system of the latter, must at present be regarded as an established fact. The conclusion drawn from this fact is, of course, that the property of producing a specific disease like tuberculosis in the organs of these animals is inherent in the bacterium tuberculosis; though the process by which the pres-

ence of this organism gives rise to the formation of tubercles in the respective tissues, is still obscure. If the production of tubercles in these animals were confined to the inoculation of those bacteria contained in tuberculous matter, the phenomenon might be easily explained by presuming this matter, and not the bacteria, to represent the specific poison. But this is not alone the case, for tubercles will still be produced in these animals by inoculating them with very remote generations of those bacteria, obtained by successive artificial cultures of those originally contained in tuberculous matter. Now, as it thus far appears to be proved, that no other species of bacteria, nor any other substance is capable of producing tubercles in an animal, when introduced into its organism by inoculation, the only satisfactory explanation of the phenomenon appears to be by presuming that the bacterium tuberculosis must have acquired this special property of producing tubercles from the tuberculous matter itself, from which it drew its nourishment during its development; that is to say, that during the development of the organism, the constituent molecules of its protoplasm arranged themselves in a similar manner as those of the tuberculous matter, on which it lived, and that it thus acquired the properties of the latter, that is of producing tubercles; and furthermore, that these properties are during the artificial cultivation of the bacteria, transmitted from generation to generation.

According to Koch the tubercle bacteria are entirely dependent upon the human and animal organisms for their existence; or in other words, they are incapable of living or reproducing out side of the latter. With reference to this assertion we may ask: where then did they originally come

from, if not from the outside world? The most plausible answer for this question may be found in the theory of "heterogenesis," according to which these organisms would originate in the elements of the specifically diseased organ itself. But the bacteria being derived from the latter, it is but natural to presume that they were also endowed with the specific properties of the diseased matter of this organ, manifesting themselves in producing "*alike*," that is, in calling forth the same pathological conditions as were present in the tissues of the respective organ, from which they were derived. In the same way all other specific contagious diseases may be explained by the theory of "heterogenesis."

Although, as may be gathered from the above, I do not deny the contagiousness of tuberculosis in cases where the specific poison is directly transferred from one organism into another, as is done in all the inoculation experiments performed on animals, it nevertheless appears to me very improbable that the numerous cases of tuberculosis in man should have originated in this manner. On the contrary, it is very doubtful that such numbers of tubercle-bacteria, as would be required to produce all these cases, are contained in the atmosphere. Koch, of course, asserts that these bacteria are derived from the expectorations of tuberculous patients, which are left on the floors of rooms or corridors, or on the ground of the streets, and which after getting dry and pulverized by the shoes of people walking over them, are disseminated throughout the air. In examining this proposition a little more closely, it will be found that, notwithstanding the prevalence of tuberculosis, a very small fraction of all the tuberculous expectoration will have a

chance to reach the atmosphere in a pulverized state. In commencing our examination among the better situated classes of society, we will find that the tuberculous patients, for the sake of cleanliness, expectorate into spitboxes instead of upon the floor, and that with the cleaning of these articles of household furniture the expectorations will eventually arrive in the sewers of the street, or in some other channel of drainage. If the patient is confined to bed, he will generally be provided with some sort of a vessel, into which he may expectorate; and if he should even make use of a handkerchief, the expectoration will hardly be allowed to dry and to be pulverized, but rather be submitted to the action of the soap-water in the washtub. The same fate the tuberculous expectorations will meet with in hospitals, though in large public institutions of this kind it may happen, now and then, that a tuberculous patient soils the floors of a corridor with his expectoration, which, however, will hardly be left to dry and to be pulverized. Hence it would be only in the lowest strata of society, where cleanliness is unknown, that tuberculous sputa might reach the atmosphere in the form of powder. In all other cases the bacteria tuberculosis, instead of being disseminated throughout the atmosphere, will ultimately arrive in the gutters and sewers of the street, to be carried to the river or ocean, where they will be incapable of living or thriving, because their existence, according to Koch, solely depends upon the human or animal organism. The same will happen to the tuberculous expectorations left on the pavements of the streets, where they will be washed away by the rains of the season. We may, therefore, presume that, as I have remarked before, but a very small fraction of all the bacteria contained in the ex-

pectorations of tuberculous patients, will ever come to float in the atmosphere. But even this small fraction, which under favorable circumstances may come to be suspended in the atmosphere, will have but very narrow chances to reach the interior of the human lungs, for the reason that, being, as just mentioned, incapable of living or of increasing their numbers by reproduction outside of the human or animal organism, they will soon be dispersed and swept away to unknown regions by the winds, or removed from the atmosphere by every rain, and like their brethren, finally arrive in the various channels of drainage.

I might still further enlarge upon this subject, but I trust that the foregoing remarks will suffice to show that the numerous cases of tuberculosis cannot be regarded as having been caused by bacteria tuberculosis floating in the atmosphere. In those rare cases in which the disease has in reality been communicated from one individual to another, it was undoubtedly accomplished by the medium of the expectoration itself, which in the form of spray—as may happen during the act of coughing or speaking or even kissing—issues from the mouth of the tuberculous individual to be inhaled by the lungs of another person. Besides the immunity from tuberculosis, generally exhibited by the resident physicians and nurses of hospitals, is another proof to show that this disease is but rarely communicated by the sole medium of the atmosphere; as an instance of this fact I simply point, as has been done by other authors before me, to the well known statistics of the “Hospital for Consumption,” at Brompton, in England.

Notwithstanding the popularity which Koch’s theory of the bacterium tuberculosis being the direct and sole cause of

tuberculosis, soon acquired after the discovery of this organism, and to a certain extent still holds, it cannot be denied that since that time, so far as may be gathered from the current medical literature, the number of those physicians who doubt the correctness of this theory, has been steadily increasing. Thus some of the most distinguished clinicians, being unable to indorse the whole original theory, have altered it in order to render it harmonious with their own practical experience, and with the old-established fact that tuberculosis is hereditary in its nature, depending upon a special diathesis which is transmitted from the parent to the offspring. Accordingly, Koch's original theory, teaching that the bacterium tuberculosis was capable of producing tuberculosis without regard to predisposition in every individual, has been modified in such a manner as to read now: *Bacterium tuberculosis produces tuberculosis when associated with tubercular diathesis, but is harmless in the absence of the latter; and vice versa, tubercular diathesis leads to tuberculosis if associated with bacterium tuberculosis, but is harmless without this organism.*

Presuming that the reader is familiar with the numerous articles, published in various medical journals, and of which the authors either advocate this theory, or even regard the bacterium tuberculosis as a product of the disease itself, I forbear to enlarge furthermore upon this subject; though I may say that the modification of Koch's original theory rather appears to me as a loss of faith in the capacity of this organism of causing the formation of tubercles. But, notwithstanding the doubts which still exist in regard to this capacity of the tubercle-bacterium, its presence in the tissues of the human lungs, or other organs, must be regarded as pathogno-

monic of the disease; though cases of tuberculosis are met with in which none of these bacteria are detected in the sputum of the patient, for the reason, that no cheesy centers, containing liberated bacteria tuberculosis, have as yet been formed.

In the foregoing treatise on the relations of the bacterium tuberculosis to the human lungs, or other organs, I have presented the subject to the reader in the light in which it has appeared to me, and, as much as possible, without any prejudice against one or the other theory concerned therein. As far as I know, I have, though unjustly, been regarded as an opponent to the theory of "living germs of disease," because I failed, as in the case of yellow fever, to detect living organisms, to which any signification concerning the cause of the disease might have been attached, in the tissues of the organs which I examined. On the contrary, I have always believed in the possibility of minute living organisms being capable of producing disease by their presence in the blood and tissues, though, in some instances, including tuberculosis, I have doubted the probability of this being the case, for the reason, that the facts, upon which the theory was based, were insufficient to explain all the phenomena manifested by the respective diseases. In those cases, however, where the observed facts covered, or explained all these phenomena, I have never hesitated to acknowledge the facts presented. But, I am unable to enthusiastically receive any new theory, founded upon one or the other observation, on mere faith, though it might be in accord with the already prevailing ideas of the day. Not being naturally inclined to enthusiasm—a passion nearly allied to fanaticism—I prefer in such cases to coolly reflect upon every detail of the subject, and, if possible, to examine it myself, before forming a definite opinion. Every new theory

should be received with caution, and not be accepted as true, before it has been thoroughly examined in all its aspects. For nearly thirty years, I have myself been engaged in original studies, but I must confess that, knowing how much every investigator is inclined to interpret some of his observations so as to correspond with one or another favorite idea, I frequently hesitate to draw conclusions from any observation, before I have thoroughly examined and considered the subject in all its aspects. During the progress of science, many theories have been formed, and subsequently abandoned upon the discovery of new and more substantial facts, that explained phenomena which the old theory failed to do. It is, therefore, not impossible, that the same may happen to the now prevailing germ-theory, and that thus the whole problem of the "germs of disease" may be solved in some at present unknown way.

EXPLANATION OF THE ILLUSTRATIONS.

Fig. 1.—Bacteria tuberculosis in tuberculous expectoration; *a*, deeply stained; *b*, feebly stained. Magnified 1090 diameters.

Fig. 2.—Bacteria met with in urine, the description of which will be found in the text.—Magnified 1,090 diameters.

Fig. 3.—Represents a small part of the periphery of a miliary tubercle with several of the neighboring non-tuberculous alveoli; *a*, shriveled nuclei containing more or less bacteria tuberculosis; *b*, epithelial cells of the non-tuberculous alveoli; *c*, inter-alveolar septa with the nuclei of their multiplied connective-tissue cells, derived from the adventitia of their vessels, etc.; *d*, small portion of the periphery of the tubercle; *e*, young tubercle, arisen from the wall of a large alveolus, or perhaps infundibular cavity, and, contrary to the

rule generally observed, has undergone the coagulation necrosis.—Magnified 625 diameters.

Fig. 4.—Represents a portion of a miliary tubercle near its cheesy centre; *a*, bacteria tuberculosis, developing in the nuclei of the tubercle cells; the outlines of the cells are not seen, on account of the object being mounted in Canada balsam and very highly illuminated; *b*, the same nuclei out of focus; *c*, inter-alveolar septa; *d*, portion of the cheesy centre of the tubercle.—Magnified about 1,090 diameters.

Fig. 5.—Represents a small portion from a large tubercle from the lungs of a boy, sixteen years old, and affected with miliary tuberculosis of the lungs, liver, spleen, kidneys, and lymphatic glands; *a*, bacteria tuberculosis, developed in the nuclei of the tubercle cells; *b*, the same out of focus; *c*, degenerated interstitial connective tissues, leading the central part of the tubercle; *d*, groups of bacteria, commencing to enlarge in their dimensions; *e*, aggregations of bacteria tuberculosis.—Magnified about 1,090 diameters.

Fig. 6.—Bacteria tuberculosis, contained in the nuclei of the muscular and of the connective-tissue cells in the wall of a bronchioles; *a*, nuclei of the connective-tissue cells; *b*, nuclei of the muscular-tissue cells.—Magnified about 1,090 diameters.

Fig. 7.—Bacteria tuberculosis contained in the nuclei of the cells of indurated tuberculous tissue.—Magnified about 1,090 diameters.

Fig. 8.—Represents a small portion of the parenchyma of the liver, bordering directly the periphery of a miliary tubercle; *a*, nuclei of hepatic cells, still presenting a normal appearance; *b*, nuclei with bacteria developing in their interior.—Magnified 625 diameters.

Fig. 9.—Represents a portion of the centre of a miliary

tubercle of the liver, having undergone coagulation-necrosis ; *a*, fissures, very likely representing the lumen of contracted capillaries ; *b*, groups of bacteria tuberculosis with the remains of the protoplasm of the nuclei, in which they were developed ; *c*, aggregations of these bacteria.—Magnified 625 diameters.

Fig. 10.—Represents some of the anatomical elements of a miliary tubercle of the liver ; *a*, group of normal hepatic cells from near the border of the tubercle ; *b*, a pair of hepatic cells from the periphery of the tubercle, the nuclei of which have commenced to shrivel ; *c*, a number of nuclei from the cheesy centre of the tubercle, the margins of which are shriveled in a higher degree and broken up into fragments ; *d*, ultimate minute fragments of nuclei, some of which have assumed the form of granular filaments.—Magnified about 1,090 diameters.

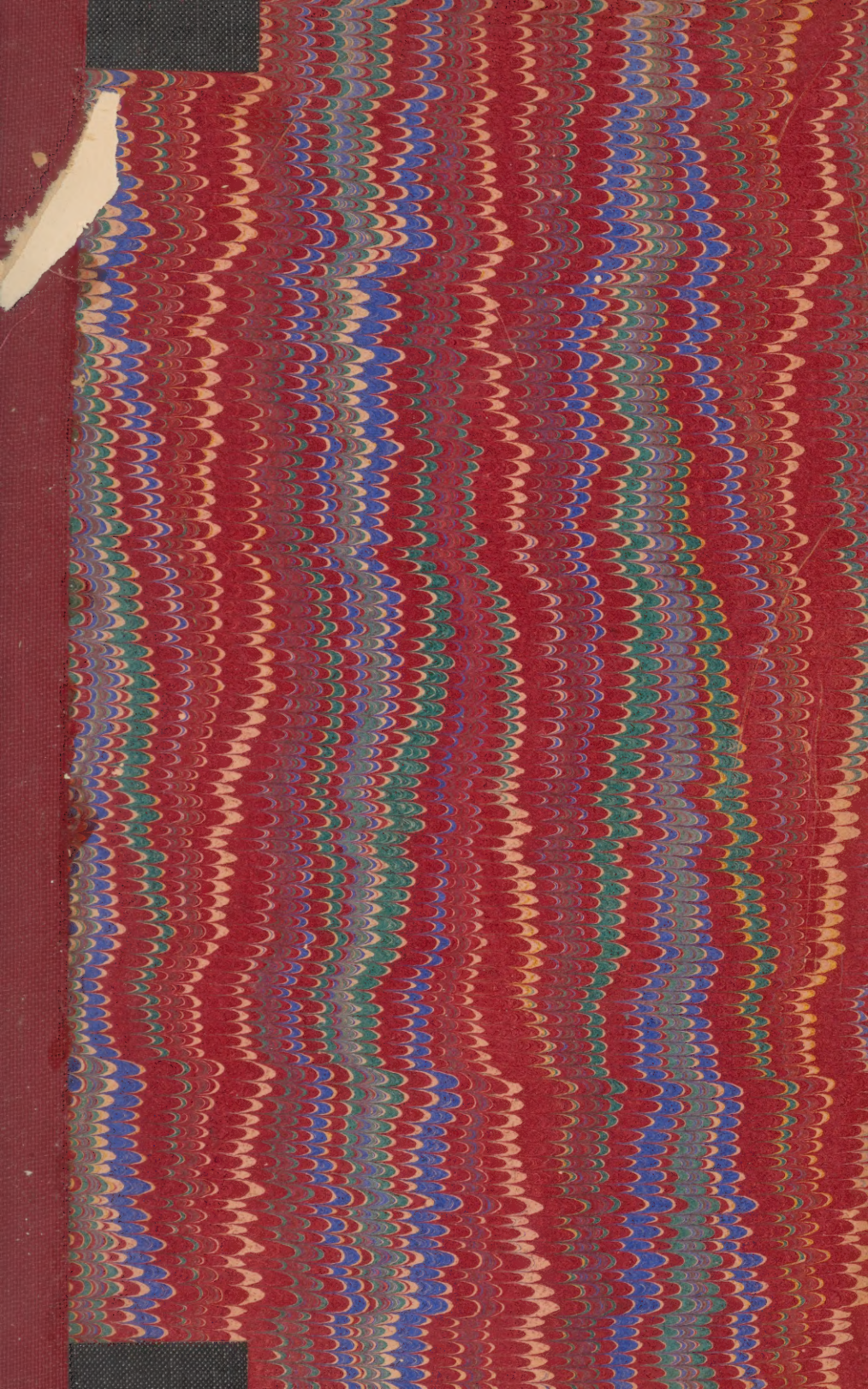
Fig. 11.—Represents a small portion of a leprous liver ; *a*, normal nuclei of hepatic cells ; *b*, degenerating nuclei with shriveled margins ; *c*, bacteria lepræ, developing in the nuclei of hepatic cells ; *d*, bacteria lepræ, liberated by the degeneration of the protoplasm of the nucleus, and disseminating throughout the likewise degenerated protoplasm of the body of the cell.—Magnified 625 diameters.

Fig. 12.—Bacteria lepræ, as met with in the blood of some lepers.—Magnified about 1,090 diameters.

Fig. 13.—Represents a minute portion of the pars reticularis of the corium of the skin from the margin of a leprous tubercle ; *a*, nuclei of connective-tissue cells containing bacteria lepræ in their early stage of development ; *b*, neoplastic connective-tissue cells in an advanced stage of fatty degeneration, containing fully developed bacteria lepræ between the fat-globules.—Magnified 625 diameters.

Fig. 14.—Represents a minute portion from the middle of the same leprous tubercle, in which the bacteria lepræ are seen in their different stages of development; *a*, bacteria in the nuclei of the unchanged connective-tissue cells; *b*, bacteria slightly more developed; *c*, the nucleus has disappeared by degeneration and the bacteria lepræ are seen fully developed in the protoplasm of the cell, exhibiting their granular nature; *d*, fully developed bacteria lepræ between the fat-globules of the degenerated cell.—Magnified 625 diameters.

Fig. 15.—A number of degenerated leprous cells higher magnified, showing to a better advantage the morphological character of the bacteria lepræ.—Magnified about 1,090 diameters.



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